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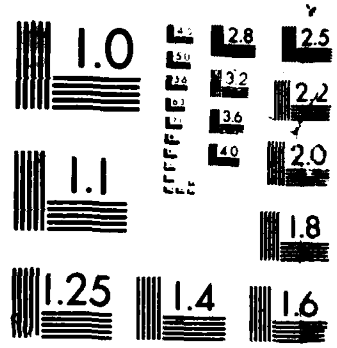

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THE USE OF ATP-$MgCl_2$ IN THE TREATMENT

OF INJURY AND SHOCK

Annual Report

IRSHAD H. CHAUDRY

July 31, 1986

Supported by
U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick
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Our objectives were to determine the safety and hemodynamic response of ATP-$MgCl_2$ infusion in normal awake human volunteers. In accordance with a protocol approved by the Human Investigation Committee, five healthy adult male volunteers received an intravenous infusion of ATP-$MgCl_2$ (0.1-0.4mg/kg/min) on four separate occasions. The total dose infused was 3, 6, 10 and 30mg/kg (n=20 studies). Hemodynamic measurements were made at end exhalation in the supine position and included heart rate and systolic, diastolic and mean blood pressure.

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Continuous electrocardiographic monitoring of lead II was performed. Cardiac output was determined by injection of indocyanine green and measured by the principle of earpiece densitometry. Measurements were made prior to infusion, at 5 minute intervals during infusion and following termination of the infusion. Blood samples were obtained for determination of hemoglobin, sodium, potassium and glucose. Stroke volume index (SVI) and total systemic resistance (TSR) were derived from standard formulae. The results indicated that cardiac output increased by 76% from control values ($p < 0.0001$) with ATP-$MgCl_2$ infusion. This increase in cardiac output correlated positively with ATP-$MgCl_2$ infusion rate ($r=0.75$, $p < 0.001$). This was paralleled by a 45% increase in heart rate ($p < 0.0001$). SVI increased by 14% (p 0.005), however, the mean blood pressure did not change significantly over the entire range of infusion rates. TSR decreased 56% at the highest rate of ATP-$MgCl_2$ infusion. A mean infusion rate of 0.32 ± 0.02mg/kg/min was associated with maximal increases in heart rate (52%) and cardiac output (119%) without affecting mean blood pressure. Hemodynamic effects were poorly correlated with total dose of ATP-$MgCl_2$ ($r=0.20$).

All hemodynamic changes returned to normal within 2 minutes after the ATP-$MgCl_2$ infusion was discontinued (p=NS). Sodium, potassium, hemoglobin and glucose levels did not change during or after ATP-$MgCl_2$ administration. All subjects experienced transient mild nausea at infusion rates greater than 0.3mg/kg/min. There were no delayed side effects.

ATP-$MgCl_2$ is a potent vasodilator. As demonstrated in this study, the increase in cardiac output offset the decrease in total systemic resistance. Thus, blood pressure (MBP) was maintained. Furthermore, the increase in SVI demonstrated a mild inotropic effect. These findings suggest that the increase in heart rate and cardiac output may depend upon an intact sympathetic nervous system. In addition, the pharmacologic profile of vasodilatation, augmentation of cardiac output, maintenance of blood pressure and mild positive inotropy coupled with beneficial effects on cell function and survival in animal studies suggest potential clinical applications of ATP-$MgCl_2$ in patients with low flow states or organ ischemia. In conclusion, data from our studies suggest a potentially beneficial role of ATP-$MgCl_2$ in the treatment of low flow states and confirms the safety of ATP-$MgCl_2$ in humans.

In additional studies, our results indicated that ATP-$MgCl_2$ infusion in normovolemic as well as hypovolemic dogs increases coronary flow and cardiac output while decreasing myocardial O_2 consumption. Thus, ATP-$MgCl_2$ does not cause any deleterious mismatch between myocardial O_2 demand and myocardial O_2 supply.

We also submitted the protocol of our Phase II studies of ATP-$MgCl_2$ to the local and the the Army's Human Investigation Committee and the protocol was approved. Infusion of ATP-$MgCl_2$ into the coronary arteries of patients undergoing routine diagnostic coronary angiography procedures produced no adverse effect in any patient coronary sinus blood flow, however, increased by 65% with a concomitant 27% reduction in myocardial O_2 consumption. The reduction in mycardial O_2 consumption in the absence of changes in the measured determinants of myocardial O_2 demand suggests a possible O_2-sparing effect of ATP-$MgCl_2$. ATP-$MgCl_2$ was also infused in patients with renal failure, severe trauma, and other adverse circulatory conditions, and the results indicated that ATP-$MgCl_2$ can be safely infused in such patients. Furthermore, the results suggest that ATP-$MgCl_2$ infsion in patients produces salutary effects.

Adenosine triphosphate-Magnesium Chloride

SUMMARY

Our objectives were to determine the safety and hemodynamic response of ATP-$MgCl_2$ infusion in normal awake human volunteers. In accordance with a protocol approved by the Human Investigation Committee, five healthy adult male volunteers received an intravenous infusion of ATP-$MgCl_2$ (0.1-0.4mg/kg/min) on four separate occasions. The total dose infused was 3, 6, 10 and 30mg/kg ~~(n=20 studies)~~. Hemodynamic measurements were made at end exhalation in the supine position and included heart rate and systolic, dyastolic and mean blood pressure. Continuous electrocardiographic monitoring of lead II was performed. Cardiac output was determined by injection of indocyanine green and measured by the principle of earpiece densitometry. Measurements were made prior to infusion, at 5 minute intervals during infusion and following termination of the infusion. Blood samples were obtained for determination of hemoglobin, sodium, potassium and glucose. Stroke volume index (SVI) and total systemic resistance (TSR) were derived from standard formulae. The results indicated that cardiac output increased by 76% from control values ~~($p< 0.0001$)~~ with ATP-$MgCl_2$ infusion. This increase in cardiac output correlated positively with ATP-$MgCl_2$ infusion rate ~~($r=0.75$, $p< 0.001$)~~. This was paralleled by a 45% increase in heart rate ~~($p<0.0001$)~~. SVI increased by 14% ~~($p\geq 0.005$)~~; however, the mean blood pressure did not change significantly over the entire range of infusion rates. TSR decreased 56% at the highest rate of ATP-$MgCl_2$ infusion. A mean infusion rate of 0.32 $\pm$ 0.02 mg/kg/min was associated with maximal increases in heart rate (52%) and cardiac output (119%) without affecting mean blood pressure. Hemodynamic effects were poorly correlated with total dose of ATP-$MgCl_2$ ~~($r=0.26$)~~.

All hemodynamic changes returned to normal within 2 minutes after the ATP-$MgCl_2$ infusion was discontinued (p=NS). Sodium, potassium, hemoblobin and glucose levels did not change during or after ATP-$MgCl_2$ administration. All subjects experienced transient mild nausea at infusion rates greater than 0.3mg/kg/min. There were no delayed side effects.

ATP-$MgCl_2$ is a potent vasodilator. As demonstrated in this study, the increase in cardiac output offset the decrease in total systemic resistance. Thus, blood pressure (MBP) was maintained. Furthermore, the increase in SVI demonstrated a mild inotropic effect. These findings suggest that the increase in heart rate and cardiac output may depend upon an intact sympathetic nervous system. In addition, the pharmacologic profile of vasodilatation, augmentation of cardiac output, maintenance of blood pressure and mild positive inotropy coupled with beneficial effects on cell function and survival in animal studies suggest potential clinical applications of ATP-$MgCl_2$ in patients with low flow states or organ ischemia. In conclusion, data from our studies suggest a potentially beneficial role of ATP-$MgCl_2$ in the treatment of low flow states and confirms the safety of ATP-$MgCl_2$ in humans.

In the Phase I studies of ATP-$MgCl_2$ in normal volunteers, most volunteers demonstrated tachycardia during infusion of this agent. It could thus be argued that tachycardia which was observed with ATP-$MgCl_2$ infusion and its attendant effects on myocardial oxygen demand may well set the stage for exacerbation of any deleterious mismatch between myocardial oxygen demand and myocardial oxygen supply. To study this, additional experiments were conducted in dogs. Our results indicated that even during hypotension ATP-$MgCl_2$ increases coronary flow and cardiac output while decreasing myocardial O_2 consumption. Although both ATP-$MgCl_2$ and nitroprusside reduced myocardial O_2 consumption through after-load reduction (decreased work), ATP-$MgCl_2$ but not nitroprusside decreases myocardial O_2 consumption for any given workload. This indicates an additional metabolic effect of ATP-$MgCl_2$. This combination of increased cardiac output with decreased myocardial O_2 consumption

supports a role for therapeutic use of ATP-$MgCl_2$ during low flow states and with coronary insufficiency. These results therefore indicate that ATP-$MgCl_2$ administration does not cause any deleterious mismatch between myocardial oxygen demand and myocardial oxygen supply.

We have also determined whether ATP-$MgCl_2$ administration has any deleterious effects on whole body oxygen consumption in dogs. The results of such experiments indicated that ATP-$MgCl_2$ infusion decreases total body oxygen consumption despite a concomitant increase in cardiac output and oxygen delivery. This could well be a metabolic effect of infused ATP-$MgCl_2$.

We also submitted the protocol of our Phase II studies of ATP-$MgCl_2$ to our Human Investigation Committee and they approved the protocol. In addition, the protocol was submitted to the Army's Human Investigation Committee and it was approved by the U.S. Army's Human Investigation Committee. We then attempted to determine the safety of ATP-$MgCl_2$ administration in six patients with coronary artery disease. ATP-$MgCl_2$ was infused into the left main coronary artery of these patients during a routine diagnostic coronary angiograph. There was no measurable effect on blood pressure, heart rate or cardiac output which all remained at baseline levels during the infusion of 0.01-0.037ml/kg/min ATP-$MgCl_2$. There were no visible contractile abnormalities during the ATP-$MgCl_2$ as monitored by two-dimensional echocardiography. In some patients coronary sinus catheters were inserted and the effects of ATP-$MgCl_2$ infusion on coronary sinus blood flow and myocardial oxygen consumption was investigated. The results demonstrated a 65% increase in coronary sinus blood flow with a concomitant 27% reduction in myocardial oxygen consumption, indicating that ATP-$MgCl_2$ is a demand-independent coronary vasodilator. The reduction in myocardial oxygen consumption in the absence of changes in the measured determinants of myocardial oxygen demand suggests a potential oxygen sparing effect of ATP-$MgCl_2$. These results therefore indicate that ATP-$MgCl_2$ can be infused safely in patients with coronary artery disease and that infusion of ATP-$MgCl_2$ up to 0.037ml/kg/min does not produce any bradycardia or decrease in blood pressure but does increase coronary sinus blood flow and decreases myocardial oxygen consumption. Thus, ATP-$MgCl_2$ shows favorable characteristics for potential applications in patients with coronary artery disease.

We have also infused ATP-$MgCl_2$ in a limited number of patients with renal failure, severe trauma, and other adverse circulatory conditions and have determined that ATP-$MgCl_2$ can be safely infused in all such patients. The results also suggest that ATP-$MgCl_2$ infusion in such patients produces salutary effects.

FOREWORD

The studies described in this report were conducted after we obtained the IND for ATP-$MgCl_2$ from the Food and Drug Administration and following the approval of our protocol from the Army's Human Investigation Committee, our local Human Investigation Committee and from the Food and Drug Administration.

For the protection of human subjects the investigator(s) have adhered to policies of applicable Federal Law 45 CFR 46.

In conducting the research described in this report, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals" prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (DHEW Publication No. (NIH) 78-23, Revised 1978).

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Body of Report

Publications

The following papers and abstract have been accepted for publication:

1. Chaudry IH, Keefer R, Barash P, Clemens MG, Kopf G, Baue AE: ATP-$MgCl_2$ (ATP) infusion in man: Increased cardiac output without adverse systemic hemodynamic effects. Surg Forum 35:14-16, 1984

2. Keefer JR, Chaudry IH, Barash PG, Clemens MG, Baue AE: ATP-$MgCl_2$: Safety and hemodynamic responses in humans. Anesthesiology 61:A119, 1984.

3. Chaudry IH: Cellular energetics and ATP-$MgCl_2$ therapy in sepsis. Am J Emerg Med 2:38-44, 1984.

4. Clemens MG, Chaudry IH, Baue AE: Increased coronary flow and myocardial efficiency with systemic infusion of ATP-$MgCl_2$. Surg Forum 36:224-226, 1985.

5. Wohlgelernter D, Jaffe C, Cleman M, Young L, Clemens MG, Chaudry IH: Effects of ATP-$MgCl_2$ on coronary blood flow and myocardial oxygen consumption. Circulation 72:III:315, 1985.

We have participated in a number of programs in which the work supported by this contract has been presented. These include presentation of our work at various national, regional and local programs on shock and circulatory failure. In addition, we presented our work supported by this contract at the American College of Surgeons' meeting and at the Annual American Society of Anesthesiology meeting.

The principle findings for the period of Sept. 1, 1984 - July 31, 1986 will now be summarized.

1. Phase I Studies of ATP-$MgCl_2$.

Since the approval of the Phase I studies by our Human Investigation Committee and the U.S. Army Medical Research and Development Command, we completed the four components of the Phase I studies. All five volunteers who had signed the consent form and participated in that study received ATP-$MgCl_2$ on four separate occasions with a total dose of 3, 6, 10 and 30mg/kg (20 studies).

The volunteers underwent a physical examination by a primary care physician prior to receiving ATP-$MgCl_2$ and they were all found to be free of any renal or cardiovascular problems. All Phase I studies were carried out in the operating room at Yale-New Haven Hospital solely for the benefit of having the facilities available in the unlikely event that ventilatory and cardiac support would be required during the study.

On the day of each study, two intravenous catheters were placed (in the forearm veins), under sterile conditions, and ATP-$MgCl_2$ was infused through one of the catheters. Blood sampling and injection of dye (indocyanine green) for cardiac output determinations were carried out through the second catheter. Each volunteer had his baseline values of sodium, potassium, glucose, hemoglobin, blood pressure, heart rate and cardiac output recorded just prior to receiving ATP-$MgCl_2$. ATP-$MgCl_2$ was infused intravenously at rates of 0.1, 0.2, 0.25, 0.28, 0.32, 0.38,

0.40 and 0.56mg/kg/min. Vital signs were recorded every 3 minutes except at the high-dose ATP-MgCl2 infusion during which they were obtained every minute. Each infusion rate was carried out, usually for ten minutes. In the final study (full dose of ATP-$MgCl_2$), however, each infusion rate was carried out for 20 or 30 minutes. Infusions were stopped for 5 minutes prior to switching to higher infusion rates. Blood samples were taken during each ATP-$MgCl_2$ infusion and cardiac output was measured using the Nihon-Kohden cardiac output computer at various ATP-$MgCl_2$ infusion rates. Five minutes after the last ATP-$MgCl_2$ infusion, blood samples were obtained and cardiac output determined in addition to recording vital signs. In addition, blood samples were obtained from volunteers one week after the administration of the full dose of ATP-$MgCl_2$ and SGOT and SGPT levels were determined. Statistical analysis was performed with ANOVA and coefficients of correlation. Statistical significance was attributed to values of $p < 0.05$.

General Observations

With the infusion of 0.1mg/kg/min ATP-$MgCl_2$ and higher, most subjects experienced a feeling of slight chest congestion, flushing in the face, overall warmness and light-headedness. The intensity of the symptoms, however, decreased with the continuation of ATP-$MgCl_2$ infusion and all of the above symptoms disappeared within a minute or two after the ATP-$MgCl_2$ infusion was stopped or completed. The mean arterial blood pressure, electrolytes, hemoglobin and serum glucose levels did not change significantly even with the continuous infusion of ATP-$MgCl_2$. The heart rate and cardiac output, however, increased with the increase in ATP-$MgCl_2$ infusion rates.

In the final study (i.e. the full dose of ATP-$MgCl_2$), most subjects experienced a feeling of chest congestion, flushing of the face, and light-headedness. The intensity of these symptoms, however, decreased during the ATP-$MgCl_2$ infusion. Most subjects also had a feeling of transient nausea if the ATP-$MgCl_2$ infusion rates were above 0.30mg/kg/min. In one subject, when the ATP-$MgCl_2$ infusion rates were increased to 0.56mg/kg/min, the subject vomited during the infusion. The rate of ATP-$MgCl_2$ infusion in the subsequent volunteers was therefore kept below 0.5mg/kg/min and none of the other volunteers had any vomiting as a result of ATP-$MgCl_2$ infusion. In addition to the above mentioned symptoms, most subjects experienced increased intestinal motility. This was probably due to the effects of ATP-$MgCl_2$ on the intestinal smooth muscle. Nonetheless, despite the small discomfort, all five subjects tolerated the ATP-$MgCl_2$ infusion and the slight discomfort they experienced during the high dose ATP-$MgCl_2$ infusions disappeared shortly after completion of the infusion. Our studies have thus indicated that ATP-$MgCl_2$ infusion is well tolerated by normal subjects, provided that the rate of infusion is not above 0.5mg/kg/min. No ventilatory or cardiac support was required in any subject during any of the ATP-$MgCl_2$ infusion studies.

Measurement of serum GOT and GPT levels before, during, at the end of ATP-$MgCl_2$ infusion and one week after the last ATP-$MgCl_2$ infusion indicated that the level of these enzymes were not affected by the administration of ATP-$MgCl_2$. In addition, there was no adverse effects of ATP-$MgCl_2$ on renal function and there were no delayed side effects of ATP-$MgCl_2$ infusion.

Effects of $ATP-MgCl_2$ infusion on heart rate

The percent increase in heart rate (HRPCT) versus $ATP-MgCl_2$ infusion rates (INFUSRT) is presented in Figure 1. The numbers 1, 2, 3, 4, and 5 represent the code for each volunteer. The results indicated that the heart rate increased with the increase in $ATP-MgCl_2$ infusion rates. There was a good correlation between $ATP-MgCl_2$ infusion rates and the increase in heart rate with an r value of 0.72 ($p < 0.001$).

Plotting the percent increase in heart rate (HRPCT) versus percent change in cardiac output (COPCT) indicated that the correlation between these two parameters was not very good (Fig. 2). The r value was found to be 0.55.

From these results, it is clear that maximal increase in heart rate was observed when $ATP-MgCl_2$ was infused at a rate of approximately 0.3mg/kg/min and with the infusion of 0.1mg/kg/min $ATP-MgCl_2$, the increase in heart rate was marginal.

The absolute heart rate virus $ATP-MgCl_2$ infusion rate is presented in Fig. 3. It is clear from this figure that only in two subjects the heart rate exceeded 130 with the infusion of 0.38mg/kg/min $ATP-MgCl_2$. With the infusion of 0.1mg/kg/min $ATP-MgCl_2$, the heart rate in any of the subjects did not increase over 100 beats/min. There was a poor correlation between the absolute heart rate and the total dose of $ATP-MgCl_2$ infused (Fig. 4). The r value in this case was found to be 0.22.

Effects of $ATP-MgCl_2$ infusion on mean blood pressure

In Figure 5 the percent change in mean blood pressure versus $ATP-MgCl_2$ infusion rates is plotted. The results indicated that there was no correlation between $ATP-MgCl_2$ infusion rates and the mean blood pressure. The r value was found to be -0.05.

There was also no correlation between the percent change in mean blood pressure and the total amount of $ATP-MgCl_2$ infused (Fig. 6). The r value was found to be 0.03.

Plotting the percent change in mean blood pressure versus percent change in cardiac output (COPCT) indicated that there was no correlation between the changes in mean blood pressure and cardiac output. The r value was found to be -0.09 (Fig. 7).

From these results, it is clear that the mean blood pressure did not change significantly with the infusion of $ATP-MgCl_2$.

Since the heart rate increased with $ATP-MgCl_2$ infusion, it could be suggested that the observed increase in cardiac output may be due to the increase in heart rate. Since there was no significant change in mean blood pressure with $ATP-MgCl_2$ infusion but cardiac output increased significantly, it indicates that $ATP-MgCl_2$ must be producing peripheral vasodilatation and the increase in the heart rate may be due to sympathetic system stimulation.

Effect on Systemic Vascular Resistance (SVR)

SVR decreased significantly with the increase in ATP-$MgCl_2$ infusion rates. The plot of SVR versus cardiac output (CO) indicates that there is a good correlation between those parameters (Fig. 8). The r value was found to be 0.89. The decreased SVR during ATP-$MgCl_2$ infusion may also be contributing to the increase of CO. Thus, the increased CO appears to be compensating for the decrease of SVR and hence maintaining the mean blood pressure during ATP-$MgCl_2$ infusion.

Effect of ATP-$MgCl_2$ on Stroke Volume Index and Other Parameters

The results presented in Table I indicate that cardiac output increased by 77% ($p < 0.0001$) at maximum infusion rate. This was paralleled by an increase in heart rate (45%, $p < 0.0001$). Stroke volume index increased by 14% ($p < 0.05$). However, the mean blood pressure did not change significantly over the entire range of infusion rates. Systemic vascular resistance decreased 56% at the highest rate of ATP-$MgCl_2$ infusion. A mean infusion rate of 0.32 ± 0.02 mg/kg/min was associated with maximum increases in heart rate (52%) and cardiac output (119%) without affecting mean blood pressure.

The results of this study demonstrate that the increase in cardiac output offset the decrease in systemic vascular resistance. Thus, blood pressure (MBP) was maintained. Furthermore, the increase in stroke volume index demonstrated a mild inotropic effect. Thus, the pharmacologic profile of vasodilatation, augmentation of cardiac output, maintenance of blood pressure and mild positive inotropy coupled with beneficial metabolic effects in animals suggests an important therapeutic role of ATP-$MgCl_2$ in the treatment of conditions characterized by regional or global ischemia.

Effects of ATP-$MgCl_2$ infusion on cardiac output

The results presented in Figure 9 are expressed as percent increase in cardiac output versus ATP-$MgCl_2$ infusion rates in mg/kg/min. As can be seen from this figure, cardiac output increased progressively with the increase in ATP-$MgCl_2$ infusion rates and there was a good correlation between the increase in cardiac output and ATP-$MgCl_2$ infusion rates. The r value was found to be 0.75 ($p < 0.001$). The correlation between percent increase in cardiac output and the total dose of ATP-$MgCl_2$ infused was not good (r=0.20) (Fig. 10). Thus, the increase in cardiac output was dependent upon the rate of ATP-$MgCl_2$ infusion but not on the total dose of ATP-$MgCl_2$ infused. From the results presented in Fig. 9, it appears that maximal increase in cardiac output in normal volunteers was obtained with the infusion of approximately 0.3mg/kg/min ATP-$MgCl_2$ and that approximately 10% increase in cardiac output was observed when ATP-$MgCl_2$ was infused at a rate of 0.1mg/kg/min.

Effects of ATP-$MgCl_2$ on sodium, potassium, blood glucose and hemoglobin concentration

The percent changes in sodium (NAPPCT) versus ATP-$MgCl_2$ infusion rates (INFUSRT) is plotted in Fig. 11 and, as can be seen, there was no correlation between the percent change in sodium and ATP-$MgCl_2$ infusion rates. The r value in this case was found to be 0.04. There was also no correlation between NAPPCT

and total dose of ATP-$MgCl_2$ infused (Fig. 12). The r value in this case was -0.12. Likewise, there was no correlation between the percent change in potassium (KPPCT) and ATP-$MgCl_2$ infusion rates (Fig. 13) and total dose (Fig. 14). The r values in these cases was found to be 0.02 and -0.12, respectively.

The percent change in glucose (GLUCPCT) versus ATP-$MgCl_2$ infusion rates is plotted in Fig. 15 and, as can be seen, there was no correlation between these two parameters. The r value in this case was found to be 0.28. Similarly, there was no correlation between GLUCPCT and total dose of ATP-$MgCl_2$ infused (r=0.16) (Fig. 16).

The percent change in hemoglobin (HBPCT) versus ATP-$MgCl_2$ infusion rate (INFUSRT) is plotted in Fig. 17 and, as can be seen, there was no correlation between these two parameters. The r value in this case was found to be 0.35. Likewise, the correlation between HBPCT and total dose of ATP-$MgCl_2$ infused was not good (r=0.26)(Fig. 18). These results therefore indicate that there were no significant changes in blood levels, sodium, potassium or hemoglobin contents with ATP-$MgCl_2$ infusion.

Effect of ATP-$MgCl_2$ infusion on serum GOT and GPT levels

Measurement of serum GOT and GPT during different rates of ATP-$MgCl_2$ infusion and at 7 days after ATP-$MgCl_2$ administration revealed that there were no changes in the levels of the above enzymes during or after ATP-$MgCl_2$ administration (Table II).

Summary of the Phase I studies

Our studies have indicated that, depending on the dose of ATP-$MgCl_2$ infusion, most subjects experienced a feeling of slight chest congestion, increased intestinal motility, flushing of the face, light-headedness and occasionally a feeling of transient nausea. The intensity of these symptoms, however, decreased with the continuation of the same dose of ATP-$MgCl_2$ infusion. All the above symptoms disappeared within a minute or two after the ATP-$MgCl_2$ was discontinued or completed. There was no significant change in mean arterial blood pressure, sodium, potassium, hemoglobin and blood glucose levels. However, the heart rate and the cardiac output increased progressively with the increase in ATP-$MgCl_2$ infusion rates. Our studies have also indicated that infusion of greater than 0.5mg/kg/min ATP-$MgCl_2$ may cause vomiting and severe discomfort and, thus, ATP-$MgCl_2$ infusions in man should be carried out below the rate of 0.5mg/kg/min. None of the volunteers required any ventilatory or cardiac support during any of the studies and all volunteers tolerated the ATP-$MgCl_2$ infusion. There were no delayed side effects of ATP-$MgCl_2$ infusion in any of the volunteers. In addition, none of the subjects requested that the study be terminated. These results have therefore demonstrated that it is safe to administer ATP-$MgCl_2$ in normal volunteers.

The results also suggest that while it is possible to administer ATP- $MgCl_2$ in normal volunteers to a rate of up to 0.4mg/kg/min without any significant adverse effects, such higher rates of ATP-$MgCl_2$ administration may not be advisable in certain subsets of patients. In patients in whom large increases in heart rate may have adverse hemodynamic effects, the rate of ATP- $MgCl_2$ infusion should be 0.1-0.2mg/kg/min. Thus, infusion of ATP-$MgCl_2$ in such patients should be carried out with monitoring of the heart rate.

In conclusion, data from this study suggest a potentially beneficial role for ATP-$MgCl_2$ in the treatment of low flow states and confirm the safety of ATP-$MgCl_2$ in humans.

2. Approval of Phase II Studies of ATP-$MgCl_2$ by our Human Investigation Committee.

We submitted the protocol to our Human Investigation Committee for their approval of ATP-$MgCl_2$ for Phase II studies. The application was reviewed by the full committee and approved.

3. Approval of our Phase II studies of ATP-$MgCl_2$ by the Army's Human Investigation Committee.

We also submitted our protocol for Phase II studies of ATP-$MgCl_2$ to the U.S. Army's Human Investigation Committee for their approval. The application was reviewed and approved.

4. Preparation of ATP-$MgCl_2$:

We have prepared all the ATP-$MgCl_2$ solutions for the Phase II studies. Such solutions were found to be sterile and pyrogen-free.

5. Food and Drug Administration.

We have requested the FDA to permit us to use yeast ATP instead of muscle ATP in our Phase II studies of ATP-$MgCl_2$. The reason for this is as follows:

In most of our previous experimental studies with ATP-$MgCl_2$ we have used the disodium ATP obtained from equine muscle. This source of ATP was used since it was considered to be the highest purity ATP available at the time we initiated our studies. Recently, Sigma Chemical Co. has been able to obtain ATP from yeast which is also 99-100% pure. Since ATP obtained from yeast is far less expensive than ATP from equine muscle, we conducted additional studies in which we compared the effects of yeast versus muscle ATP on hepatic mito- chondrial function and blood flow following hepatic ischemia. The results indicated that the improvement in mitochondrial function as well as in hepatic blood flow following ischemia and treatment with yeast or muscle ATP was the same. Thus, it is clear that the beneficial effects of ATP-$MgCl_2$ following adverse circulatory conditions are not dependent on the source of ATP. The efficacy of yeast ATP is of potentially far-reaching practical importance since we are in the process of initiating a large number of clinical studies with ATP-$MgCl_2$. Although the isolation of ATP from equine muscle has been adequate to meet the needs imposed by research demands, there may be limitations for large-scale production for clinical use. Yeast ATP, on the other hand, can be produced in large quantities by phosphorylation of adenosine by yeast and has the added advantage of being far less expensive than ATP isolated from equine muscle. Thus, the use of this source of ATP would make potential ATP-$MgCl_2$ treatment far more cost-effective.

6. Effect of ATP-$MgCl_2$ on myocardial O_2 consumption and coronary blood flow.

In the Phase I studies of ATP-$MgCl_2$ infusion in normal volunteers, most

volunteers demonstrated tachycardia during the infusion of this agent. It could thus be argued that tachycardia which was observed with ATP-$MgCl_2$ infusion and its attendant effects on myocardial oxygen demand may well set the stage for exacerbation of any deleterious mismatch between myocardial oxygen demand and myocardial oxygen supply. Thus, the potential results could be dysrhythmias, myocardial ischemia, myocardial infarction or all three. Since the Phase I studies of ATP-$MgCl_2$ did not eliminate this possibility, we found it necessary to conduct additional animal experiments to determine whether or not ATP-$MgCl_2$ increases myocardial O_2 consumption. To study this, 9 closed-chest, mongrel dogs were anesthetized with Nembutal and instrumented with a BAIM catheter in the coronary sinus for measurement of coronary flow (CF) and sampling of coronary sinus blood and a Swan Ganz catheter for cardiac output (CO) measurement. Arterial blood pressure was monitored via catheter in the femoral artery. ATP-$MgCl_2$ (mg/kg/min) or Nitroprusside (NP) (ug/kg/min) were infused into a femoral vein. In additional experiments, dogs were made hypovolemic (mean arterial pressure (MAP) of 80 $\pm$ 5mmHg) and the ATP-$MgCl_2$ infusion repeated. All results are normalized to percent of the immediately preceding baseline values. The results of coronary flow, myocardial oxygen consumption (MVO_2), mean arterial pressure, cardiac output and an estimate of myocardial energy cost (MVO_2/heart rate x peak systolic pressure) were:

Infusion Rate	CF	MVO_2	MAP	CO	Energy Cost
ATP-$MgCl_2$					
0.6	123 $\pm$ 19	59 $\pm$ 11	81 $\pm$ 3	154 $\pm$ 16	74%
1.2	245 $\pm$ 15	53 $\pm$ 9	70 $\pm$ 3	143 $\pm$ 8	74%
2.5	182 $\pm$ 24	39 $\pm$ 3	60 $\pm$ 4	131 $\pm$ 6	67%
2.5 (Hypovolemic)	198 $\pm$ 50	63 $\pm$ 22	57 $\pm$ 1	120 $\pm$ 5	98%
Nitroprusside					
5	88 $\pm$ 10	80 $\pm$ 15	76 $\pm$ 6	118 $\pm$ 12	110%
10	130 $\pm$ 40	87 $\pm$ 16	65 $\pm$ 5	120 $\pm$ 13	143%
20	95 $\pm$ 9	51 $\pm$ 6	45 $\pm$ 6	85 $\pm$ 3	94%

These results demonstrate that, even during hypotension, ATP-$MgCl_2$ increases CF and CO while decreasing MVO_2. Although both ATP-$MgCl_2$ and NP reduced MVO_2 through after-load reduction (decreased work), ATP-$MgCl_2$ but not NP decreases MVO_2 for any given workload. This indicates an additional metabolic effect of ATP-$MgCl_2$. This combination of increased CO with decreased MVO_2 supports a role for therapeutic use of ATP-$MgCl_2$ during low-flow states and with coronary insufficiency. The results presented above therefore clearly indicate that ATP-$MgCl_2$ administration does not cause any deleterious mismatch between myocardial oxygen demand and myocardial oxygen supply.

7. Effect of ATP-$MgCl_2$ infusion on total body oxygen consumption and hemodynamics.

We have also determined whether ATP-$MgCl_2$ administration has any deleterious effects on total body oxygen consumption. To study this, six adult mongrel dogs were anesthetized with sodium pentabarbitol using a 20mg/kg initial bolus and a 5mg/kg/hr constant infusion. They were ventilated on a Harvard respirator set at a tidal volume of 5cc/kg and a respirator rate of 10-12/min. Hemodynamic and respiratory parameters were monitored using indwelling pulmonary artery, femoral artery and femoral vein catheters and a Beckman metabolic cart, respectively. After baseline measurements were obtained, ATP-$MgCl_2$ was infused at rates from 0.32mg/kg/min to 2.56mg/kg/min. Comparing baseline data and data obtained during

the highest infusion rate, systemic vascular resistance (mean SE) (dyn-sec-cm^{-5}) decreased from 4,720 + 853 to 2,010 $\pm$ 1021 ($P < 0.02$ by the paired t-test). Mean arterial pressure (mmHg) decreased from 159 $\pm$ 4 to 97 + Heart rate decreased from 164 $\pm$ 14 to 124 $\pm$ 14 ($P < 0.01$). Cardiac output (L/min) by the Fick method, increased from 3.01 + 0.42 to 3.87 $\pm$ 0.44 ($P < 0.01$). Oxygen pulse (ml/beat) increased from 0.79 $\mp$ 0.07 to 0.95 $\mp$ 0.09 ($P < 0.01$) and oxygen delivery (ml/min) increased from 590 $\pm$ 102 to 750 $\pm$ 114 ($P < 0.01$). There was no significant change in pulmonary vascular resistance, pulmonary capillary wedge pressure or right atrial pressure. Oxygen consumption (ml/min) decreased from 127 $\pm$ 9 to 114 $\pm$ 11 ($P < 0.005$) while carbon dioxide production did not change. Arterial blood gases showed no significant change in pH or PCO_2 but PO_2 (mmHg) increased from 102 $\pm$ 2 to 111 + 3 ($P < 0.01$), due to an increase in mixed venous PO_2 from 42 $\pm$ 2 to 52 $\pm$ 1 ($P < 0.01$) We conclude that ATP infusion decreases oxygen consumption despite a concomitant increase in cardiac output and oxygen delivery. This could well be a metabolic effect of infused ATP-$MgCl_2$.

8. Phase II Studies of ATP-Mg.

We evaluated the safety of ATP-$MgCl_2$ administration in six patients with coronary artery disease. ATP-$MgCl_2$ infusion was carried out into the left main coronary artery of such patients during routine diagnostic coronary angiography procedures. Concentrations of 0.01 mg/kg/min infused over a 5 minute period were tolerated without symptomatic effects on each patient. There was no measurable effect on blood pressure, heart rate or cardiac output which all remained at baseline levels. There was no visible contractile abnormality during the ATP-$MgCl_2$ infusion as monitored by two-dimensional echocardiography.

Concentrations of 0.05 mg/kg/min in one patient (who was diabetic) produced a minor fall in blood pressure of approximately 10mmHg, bradycardia (heart rate falling from 80 beats/min to 60 beats/min) and was accompanied by the subject feeling chest congestion. The bradycardia and symptomology disappeared promptly (within seconds) upon cessation of the drug infusion (which we had been infusing for up to 2 minutes). In all the other patients the infusion rate was kept below 0.04 mg/kg/min and there was no decrease in blood pressure, bradycardia or any evidence of ischemia during ATP-$MgCl_2$ infusion.

In three patients, coronary sinus catheters were inserted and the effects of ATP-$MgCl_2$ infusion on coronary sinus blood flow and myocardial O_2 consumption were investigated. ATP-$MgCl_2$ in such patients was infused into the left coronary artery at rates from 0.01 - 0.37 mg/kg/min. The results indicated that heart rate, blood pressure, cardiac output and pulmonary capillary blood pressure remained unchanged from pre-infusion values. The results (mean $\pm$ SE) of coronary sinus blood flow, myocardial O_2 consumption and coronary vascular resistance were as follows:

	CSBF	MVO_2	CVR
Pre-ATP-$MgCl_2$ Infusion:	178 $\pm$ 11 ml/min	14.9 $\pm$ 2.9 cc/min	0.6 $\pm$ 0.01
During ATP-$MgCl_2$ Infusion:	293 $\pm$ 30 ml/min*	10.9 $\pm$ 2.2 cc/min*	0.36 $\pm$ 0.01*

*$p < 0.05$ compared to pre-ATP-$MgCl_2$ infusion.

CSBF = Coronary sinus blood flow
MVO_2 = Myocardial O_2 consumption
CVR = Coronary vascular resistance

These data demonstrate a 65% increase in coronary sinus blood flow with a concomitant 27% reduction in myocardial O_2 consumption, indicating that ATP-$MgCl_2$ is a demand-independent coronary vasodilator. The reduction in myocardial O_2 consumption in the absence of changes in the measured determinants of myocardial oxygen demand suggest a possible oxygen-sparing effect of ATP-$MgCl_2$. These results therefore indicate that ATP-$MgCl_2$ can be infused safely in patients with coronary artery disease and that infusion of ATP-$MgCl_2$ up to 0.037 mg/kg/min does not produce any bradycardia or decrease in blood pressure but does increase coronary sinus blood flow and decreases myocardial O_2 consumption. Thus, ATP-$MgCl_2$ shows favorable characteristics for potential application in patients with coronary artery disease.

ATP-$MgCl_2$ in Patients with Acute Renal Failure.

A 71-year-old female patient underwent diagonstic angiography procedure with dye injection following which she went into renal failure. The next day she had the coronary artery bypass graft while still having acute renal failure. Her urine output was approximately 5 ml/hr. The patient was also severely diabetic and had gangrenous toes. We infused ATP-$MgCl_2$ twelve hours after the bypass surgery at a rate of 0.104 mg/kg/min and there was no adverse symptomology with that infusion. We then increased the infusion rate to 0.204 mg/kg/min ATP-$MgCl_2$ and that, too, was tolerated equally well. The infusion rate was then increased to 0.26 mg/kg/min ATP-$MgCl_2$ without any adverse effects. The cardiac output prior to infusion was 3.8 L/min and it increased to 5.1 L/min during ATP-$MgCl_2$ infusion. The patient received the entire dose of ATP-$MgCl_2$ and during the infusion the urine output went up to approximately 25 ml/hr. One hour after the infusion was completed, her urine output was 120 cc/hr. We then gave a second dose of ATP-$MgCl_2$ during which the cardiac output stayed elevated to approximately 5 L/min and urine output was also somewhat increased. The patient was stable thereafter for at least 5 days at which time the observations were terminated.

Another elderly woman, post-coronary artery bypass graft, developed acute renal failure immediately post-operatively. At the time of the operation, the patient had transection of her old coronary artery bypass grafts during performance of the sternotomy. It was necessary, therefore, to place this patient on bypass immediately. She had multiple adhesions between the pericardium and heart that needed to be lysed during the operation. Because of these multiple problems, the patient required a massive amount of blood transfusion. At no time was the patient felt to be significantly hypotensive and in cardiac shock. However, at the completion of the operation, the patient had a cardiac index of approximately 1.6. The patient was brought to the recovery room and stablized. She was placed on Dopamine, Nipride and Apresoline. The patient's cardiac function improved steadily and her cardiac index increased to greater than 2.4. However, at this time, the patient became relatively oliguric. During the first hours of recovery, the patient had 5 to 10 ml of urine output per hour. She had a transient increase in her urine output in response to diuretics. However, her urine output fell to 5 to 10 ml/hr again soon thereafter. A creatinine drawn at this time showed an increase of 1.4 preoperatively to 1.7. In addition, her BUN increased from less than 20 preoperatively to 22 post-operatively. She did not respond to the second dose of diuretics. At this time, she had adequate cardiac output. A repeat of urine-lytes and serum-lytes were drawn. The patient had a normal potassium but showed an increase in her BUN to 22 and creatinine to 2.2. The patient was then started on 0.05 mg/kg/min ATP-$MgCl_2$. At this dose, there was a minimal hypotensive effect which was reversed by decreasing the patient's Nipride and Apresoline. There was no increase in the patient's heart rate. We then increased the ATP-$MgCl_2$

infusion rate to 0.1 mg/kg/min and again a hypotensive effect was observed. This was eliminated by stopping Apresoline and Nipride and the patient maintained a blood pressure of 110/70. The patient's cardiac output remained stable with a cardiac index of greater than 3. Eight hours after initiation of ATP-$MgCl_2$ infusion, the patient began to diurese. Her urine output increased from 5-10 ml/hr to greater than 30 ml/hr. This level of urine output was maintained for 5 hrs until the patient was given a dose of Edecrin (50 mg) and Aminophylline (250 mg). The patient had brisk diruesis in response to the diuretics with a urine output of 500 ml/hr. There was also a slight drop in the creatinine from 2.2 to 2. There was a slight increase in BUN from the mid 20s to 32. The patient continued to diurese throughout the day in spite of not receiving any further diuretics. After her initial diuresis, in response to the diuretics, she continued to diurese approximately 60 ml/hr throughout the remainder of the day. Approximately 24 hrs after the initiation of ATP-$MgCl_2$, the creatinine further decreased from 2.2 to 1.8. The infusion of ATP-$MgCl_2$ was completed after approximately 10 hrs. Thirty-six hours after the initiation of ATP-$MgCl_2$ infusion, the creatinine continued to fall but there was a slight further increase in BUN throughout, thought to be secondary to hypovolemia. Urine output remained between 30 and 60 cc/hr and again no further diuretics were administered. During the 5 day follow-up after the initiation of ATP-$MgCl_2$ infusion, the patient's creatinine continued to fall to a level of 1.5 which was essentially unchanged from the pre-operative values. The patient's BUN also fell to approximately 28. Urine output continued approximately at 30 ml/hr and, hemodynamically, the patient remained with a good cardiac output and was weaned off of the inotropes by the second post-operative day. During late follow-up of the patient, she had had no rebound increases in her BUN and creatinine and had remained with adequate urine output. These results indicate that ATP-$MgCl_2$ can be infused safely in patients with acute renal failure and also suggest that its administration accelerates the recovery of renal function following acute renal failure.

ATP-$MgCl_2$ Infusion in Trauma Patients.

a) Motorcycle Accident: A 24 years old man had a motorcycle accident and he was brought into the hospital with MAST trowsers and with a blood pressure of 80 mmHg. The patient was somehow volume-overloaded in the emergency room and he went into cardiac arrest. He was resuscitated and intubated in the E.R., however, because of the large amount of fluid that he had received, he developed pulmonary edema, renal failure and hepatic failure. His SGOT levels were 12,000 IU and creatinine levels over 5 although his urine output was reasonable.

We infused ATP-$MgCl_2$ in this patient at a rate of 0.123 mg/kg/min. The patient was conscious and he did not complain of any adverse effects. Ten minutes later, we increased the infusion to 0.246 mg/kg/min and he tolerated that infusion rate also without any complications. His cardiac output during ATP-$MgCl_2$ infusion increased from 6 to 9 L/min and a second blood sample drawn at the end of the ATP-$MgCl_2$ infusion revealed that the SGOT levels had decreased to 5,000 IU. The creatinine levels did not decrease immediately but a day later they were significantly lower and the patient was discharged approximately five days thereafter at which time hepatic, renal as well pulmonary function was normal. This study therefore indicates that ATP-$MgCl_2$ can be infused safely in patient's with pulmonary edema, acute renal failure and hepatic failure.

b) Gunshot Wound of the Abdomen with Low Cardiac and Urine Output.

This patient was shot in the chest and abdomen and underwent an exploratory thorocotomy through a median sternotomy and an exploratory laparotomy. During the operation, she was extremely hypotensive, requiring cardiac massage. Post-operatively, she was returned to the Surgical Intensive Care Unit where she remained in hypovolemic shock. She had active bleeding, requiring multiple transfusions of blood. She was also receiving Dopamine and had a cardiac index of approximately 1.7 L/min. Her pulse rate was approximatey 130 and she had no urine output and continued to be hypotensive. She was started on ATP-$MgCl_2$ at 0.1 mg/kg/min and her heart rate increased to approximately 150 beats/min. During the ATP-$MgCl_2$ infusion, her cardiac index increased to 3 L/min and cardiac output to approximately 5.8 L/min. She continued to receive ATP-$MgCl_2$ at a rate of 0.1 mg/kg/min for approximately 8 hours, at which time the dose was increased to 0.15 mg/kg/min. Her pulse was stable at approximately 120. She started to make urine and her blood pressure began to improve. She did, however, require continuous transfusion of blood and blood products. This patient was maintained on ATP-$MgCl_2$ infusion for approximately 36 hrs, at which time the infusion was stopped. Her cardiac output remained stable while on ATP-$MgCl_2$ and her urine output increased significantly during and following ATP-$MgCl_2$ infusion. The bleeding stopped and the patient did very well with a stable cardiac index and a stable blood pressure. The patient was subsequently discharged from the hospital and she continued to do well. These results therefore indicate the safety of continuous ATP-$MgCl_2$ infusion even over a prolonged period of time.

Patient Requiring Emergency Aortobifemoral Graft With Low Cardiac Output and Urine Output.

A 70-year-old lady was admitted to the hospital with acute occlusion of an axillary femoral graft. At that time it was elected to perform an emergency aortobifemoral bypass on this patient. She was taken to the operating room where this was done and, intra-operatively, she had a cardiac arrest. She had four episodes of ventricular fibrillation requiring defibrillation. At the conclusion of the operation, she was extremely hypotensive. She was taken to the Surgical Intensive Care Unit on Lidocaine, Dopamine and Isoprel drips. During her first 12 hrs in the ICU, she continued to require inotropic support. Her cardiac index was approximately 2.1 and her blood pressure was approximately 120/60. Her pulse rate was 120 but her urine output was approximately 7.5 ml/hr. ATP-$MgCl_2$ infusion was started 24 hrs after the operation. At that time the ATP-$MgCl_2$ was started, she was receiving 5mcg/kg/min of Dopamine, 14 drops/min Nipride and also Lasix drip (10mg/hr). She was started on 0.1 mg/kg/min ATP-$MgCl_2$, at which time her cardiac output was 4.2 L/min and her cardiac index was 2.5 L/min. After ATP-$MgCl_2$ infusion was begun, her cardiac output increased to 5.56 L/min and her cardiac index increased to 3.43 L/min. Her pulse remained stable at 117 and her blood pressure also remained at 120/60. Her urine output at the time she was started on ATP-$MgCl_2$ had been for the previous hour, 10 ml/hr. When she started receiving the ATP-$MgCl_2$, her urine output was 10 cc/hr for the first hour and then increased to 31 ml/hr for the next hour. She was maintained on 0.1 mg/kg/min ATP-$MgCl_2$ for 6 hrs. After 6 hrs, the ATP-$MgCl_2$ infusion was increased to 0.15 mg/kg/min. Her cardiac output remained elevated and her heart rate continued to also be stable at approximately 114 beats/min with a stable blood pressure of 120/60. Her urine output increased to approximately 100 ml/hr when the ATP-$MgCl_2$ infusion was increased to 0.15 mg/kg/min. She remained on this dose for 6 hrs, following which ATP-$MgCl_2$ infusion was stopped. At the time the ATP-$MgCl_2$ infusion was completed the cardiac output was 5.29 L/min and the cardiac index was

3.26 L/min. The BUN at the time of initial ATP-$MgCl_2$ infusion was 19 with a creatinine of 2.1. When the ATP-$MgCl_2$ was completed, her BUN was 32 with a creatinine of 2.8. During the next two days, the patient's urine output increased progressively to approximately 250 ml/hr. During the next day after the ATP-$MgCl_2$ had been infused, her urine output was 4,000 ml. The BUN and creatinine rose slowly. Her BUN plateaued at the level of 40 with a creatinine of 2.5, these values decreased thereafter. Through the course of the next few days, the urine output decreased to approximately 2,500 ml/24 hrs. This woman continued to be hemodynamically stable and was subsequently transferred out of the ICU.

ATP-$MgCl_2$ Infusion in an End-Stage Heart Disease Patient (Left Ventricular Assist Device, Low Cardiac Output and Urine Output).

A 27-year-old man with a testicular lymphoma had been treated with chemotherapy. He received Adriamycin and developed cardiac toxicity secondary to this. Because of the intractable cardiac failure, he was placed on left ventricular assist device (LVAD). After this, he developed acute renal failure despite the fact that he was getting numerous inotropic drugs such as Apresoline (0.1 mg/kg/min), Dopamine (11 mcg/kg/min), Debutamine (7 mcg/kg/min), Nipride (15 drops/min), Lidocaine drip at 1 mg/min, Isoprel at 0.08 mcg/kg/min and Levophed at 0.038 mcg/kg/min. His cardiac index at this time was approximately 4.4 L/min. His blood pressure was approximately 120/60 with a heart rate of 128. His urine output prior to receiving ATP-$MgCl_2$ was 15 ml/hr and his BUN was 33 with a creatinine of 2.7. He received ATP-$MgCl_2$ at a rate of 0.066 mg/kg/min which caused his blood pressure to decrease by 20 mm Hg. The ATP-$MgCl_2$ infusion was therefore decreased to 0.05 mg/kg/min and he tolerated this infusion rate very well. His blood pressure was 120/50 and pulse remained at 122. RA pressure remained at 24 and LA pressure at 11 mm Hg. His cardiac output remained at 4.5 L/min and his urine output continued to be low. He received the entire dose of ATP-$MgCl_2$ (2.4g ATP and 0.8g $MgCl_2$) in approximately 12 hrs, and during the entire course of the infusion, his blood pressure remained steady, as did the rest of his hemodynamic parameters. During the time that he was receiving the ATP-$MgCl_2$, he was taken off the Apresoline and the Nipride because of the vasodilation caused by ATP and also because of the drop in his blood pressure. Consequently at the end of the ATP-$MgCl_2$ infusion, he was still on Dopamine, Debutamine, Lidocaine, Levophed and Isoprel at the dosages stated above. At the end of the infusion, his urine output was still low but after the infusion was completed, his urine output began to increase. The last hour that he was on ATP-$MgCl_2$, his urine output was 50 ml/hr. His BUN at the time the ATP-$MgCl_2$ was stopped was 33 with a creatine of 2.6. He also had a decrease in his cardiac output. When the ATP was stopped, his cardiac output decreased from 4.27 L/min to 3.42 L/min. Consequently, he was started on Nipride. With Nipride, his cardiac output did not increase and his blood pressure also did not dercease. Over the course of the next 12 hours, after the ATP had been stopped, his urine output was approximately 1,500 cc. Urine output then increased dramatically and he was making approximately 100 cc/hr. Over the course of the next 24 hrs, his urine output was 4.5 L and his BUN was 34. His creatinine, however, decreased to 1.8. This patient therefore showed a good response to ATP-$MgCl_2$ infusion. While the ATP-$MgCl_2$ was being infused, his urine output was low but after the ATP was stopped, his urine output increased dramatically and he went into what appeared to be a high output ATN, making approximately 4.5 L over the next 24 hrs. BUN and creatinine plateaued and then came down. Hemodynamically, he was stable and, over the course of the next two days, he was able to be weaned off most of his inotropic drips. The only problem encountered was, initially, hypotension and Apresoline and Nipride was stopped and the ATP-$MgCl_2$ infusion was infused at a lower rate, in order for his blood pressure to tolerate it. Otherwise, there were no problems encountered in infusing ATP-$MgCl_2$ and he obviously benefitted from it.

$ATP\text{-}MgCl_2$ in Patients with Subendocardial Myocardial Infarction.

Following a six-vessel bypass grafting using saphenous veins, the female patient had difficulty coming off the cardiopulmonary bypass and required considerable pharmacologic support in addition to intra-aortic balloon pump. The inotropic agents included Dopamine, Dobutamine, Isoproterenol and Epinephrine. The patient was also receiving vasodilators including Nitroprusside and Apresoline. In spite of this intensive care, she continued to have a cardiac output of less than 2 L/min and a cardiac index of approximately 1.8. On the second post-operative day, because of ischemia of the right lower extremity, it became necessary to remove the intra-aortic balloon pump and carry out embolectomy of the femoral artery. The balloon pump was to be inserted in the other side. During this critical period in change of the pump, we infused $ATP\text{-}MgCl_2$. At the time of the beginning of the infusion of $ATP\text{-}MgCl_2$, her mean arterial blood pressure was 50 and she had a cardiac index of 1.8. Her heart rate was approximately 110 but that was being provided by intraventricular pacing. Mixed venous oxygen saturation was 44 and following the infusion of $ATP\text{-}MgCl_2$ there was no change in the mean arterial blood pressure or heart rate. Where was a slight improvement in the mixed venous O_2 saturation from 44 to 48%. After approximately 5 min administration of $ATP\text{-}MgCl_2$, at 0.1 mg/kg/min, the rate was increased to 0.2 mg/kg/min. At this dose there was a slight decrease in mean arterial blood pressure and a fall in the mixed venous O_2 saturation. Therefore, the infusion was decreased back to 0.1 mg/kg/min. There were multiple procedures performed on the patient during the administration of $ATP\text{-}MgCl_2$. Blood pressure during this period ranged from 85/60 to 90/60 and heart rate ranged from 97-110. Cardiac output was approximately 2.6. It increased shortly after $ATP\text{-}MgCl_2$ was started to 3.41 L/min and stayed at approximately that level during the infusion. Cardiac index reached a high of 2.0 during the infusion. Following cessation of the $ATP\text{-}MgCl_2$, blood pressure increased somewhat, reaching a high of 110/70 but in spite of this, cardiac output progressively decreased thereafter. The patient died approximately 12 hours after the cessation of the drug in spite of massive pharmacological support by all available means. Her death occurred approximately 48 hrs following the operation because of low cardiac output and inadequate function of the left ventricle. At autopsy, this patient was found to have 100% occlusion of the right coronary artery, 80% occlusion of the left coronary artery, 100% occlusion of the left anterior descending artery and 60% proximal occlusion of the circumflex. There was cardiomegaly and left ventricular hypertrophy. The patient had a myocardial infarction previously and also a recent myocardial infarction involving the posterior left ventricle and septum. There was evidence of congestive heart failure and changes throughout the various organs. Although this patient did not survive because of severe coronary artery disease, it was clear that $ATP\text{-}MgCl_2$ infusion was safe even in such patient and that there was an increase the cardiac output during the infusion of this complex.

$ATP\text{-}MgCl_2$ in Patients with Hepatorenal Syndrome.

A 65-year-old man underwent a right hepatic resection for hepatocellular carcinoma. He had a difficult post-operative course and developed the hepatorenal syndrome. Approximately three weeks post-operatively, he continued to be relatively oliguric and had increaseing BUN and creatinine. At the time of initiation of $ATP\text{-}MgCl_2$ infusion, he was hemodynamically stable with a cardiac index of 3.49 and a mean blood pressure of 85 mmHg. His heart rate was 98. BUN and creatinine, prior to $ATP\text{-}MgCl_2$ administration, was 110 and 5.4, respectively. The $ATP\text{-}MgCl_2$ was then begun at a rate of 0.1 mg/kg/min. After administration of $ATP\text{-}MgCl_2$, the mean arterial blood pressure slightly decreased,

however, there was no change in heart rate. The cardiac output increased from 3.49 to 4.17. Prior to ATP-$MgCl_2$ infusion, hourly urine output was approximately 5 ml/hr and during ATP-$MgCl_2$ infusion, it remained the same. The ATP-$MgCl_2$ infusion was then increased to 0.2 mg/kg/min. This infusion was continued for 6 hours. After completion of the ATP-$MgCl_2$ infusion, the BUN and creatinine were essentially unchanged at 114 and 5.4, respectively. During the ensuing 48 hours, his urine output continued to be minimal. He eventually required hemodialysis. The patient continued to have a difficult post-operative course with multiple medical problems. He had continued worsening of hepatic failure and eventually died of hepatic insufficiency several weeks after the infusion. Although the ATP-$MgCl_2$ did not result in improved renal function, there was an increase in cardiac output during the infusion and no deleterious effects with ATP-$MgCl_2$ were observed.

In view of the information presented above, it is clear that ATP-$MgCl_2$ can be safely infused intravenously in patients with acute renal failure, severe trauma, with low cardiac output, subendocardial myocardial infarction, hepatorenal syndrome, end-stage heart disease and even directly into the coronary arteries of patients with marked coronary artery diseases. We now plan to conduct the Phase III studies of ATP-$MgCl_2$ and presented below are our protocols for those studies.

TABLE I. EFFECT OF ATP-$MgCl_2$ ON CARDIAC OUTPUT AND PERIPHERAL VASCULAR RESISTANCE

ATP-$MgCl_2$ Infusion rate (mg/kg/min)	Heart Rate	Mean Blood Pressure	Cardiac Output	SVI	SVR
0 - 0.01 (Group 1)	74.3±1.6	92.3±1.0	7.7±0.4	0.057±0.002	12.2±0.53
0.10 - 0.19 (Group 2)	72.3±3.2	91.6±2.0	9.0±1.0	0.062±0.004	11.5±1.18
0.22 - 0.28 (Group 3)	97.7±2.9***	91.1±1.8	12.8±0.6***	0.068±0.003**	7.3±0.72***
0.31 - 0.40 (Group 4)	107.3±3.6***	93.6±2.3	13.6±0.7***	0.065±0.003*	6.8±0.83***

***$p < 0.0001$ compared to Group 1
**$p < 0.004$ compared to Group 1
*$p < 0.05$ compared to Group 1

Cardiac output and peripheral vascular resistance measurements in each of the 5 volunteers at 4 separate occasions were performed in the absence and presence of various rates of ATP-$MgCl_2$ infusion. Values are mean ± S.E. SVI = Stroke Volume Index, SVR = systemic vascular resistance. Statistical analysis were performed with ANOVA and co-efficients of correlation.

TABLE II. EFFECT OF $ATP\text{-}MgCl_2$ INFUSION ON SERUM GOT AND GPT LEVELS (KARMAN UNITS/ML)

3rd $ATP\text{-}MgCl_2$ INFUSION SERIES

		Volunteer # 1	2	3	4	5
Pre-$ATP\text{-}MgCl_2$ Infusion	GOT	12.19	14.38	15.37	29.90	16.25
	GPT	11.66	5.43	5.83	26.0	9.75
$ATP\text{-}MgCl_2$ INFUSION RATE		0.37mg/kg/min	0.37mg/kg/min	0.37mg/kg/min	0.33mg/kg/min	0.4mg/kg/min
During $ATP\text{-}MgCl_2$ Infusion	GOT	14.84	14.31	10.07	28.60	17.55
	GPT	14.31	5.83	6.36	24.70	7.80
7 days Post $ATP\text{-}MgCl_2$ Infusion	GOT	18.02	14.30	16.90	26.40	15.85
	GPT	12.72	5.85	7.15	25.30	8.82

4th $ATP\text{-}MgCl_2$ INFUSION SERIES

		Volunteer # 1	2	3	4	5
Pre-$ATP\text{-}MgCl_2$ Infusion	GOT	12.50	20.82	18.62		17.40
	GPT	4.00	6.25	5.62		10.02
$ATP\text{-}MgCl_2$ INFUSION RATE		0.23mg/kg/min	0.37mg/kg/min	0.32mg/kg/min		0.2mg/kg/min
During $ATP\text{-}MgCl_2$ Infusion	GOT	16.90	18.00	17.50	SAMPLES	14.50
	GPT	7.80	5.62	5.00	HEMOLYZED	10.02
7 days Post $ATP\text{-}MgCl_2$ Infusion	GOT	13.80	17.60	16.85		17.65
	GPT	8.01	5.75	5.35		10.80

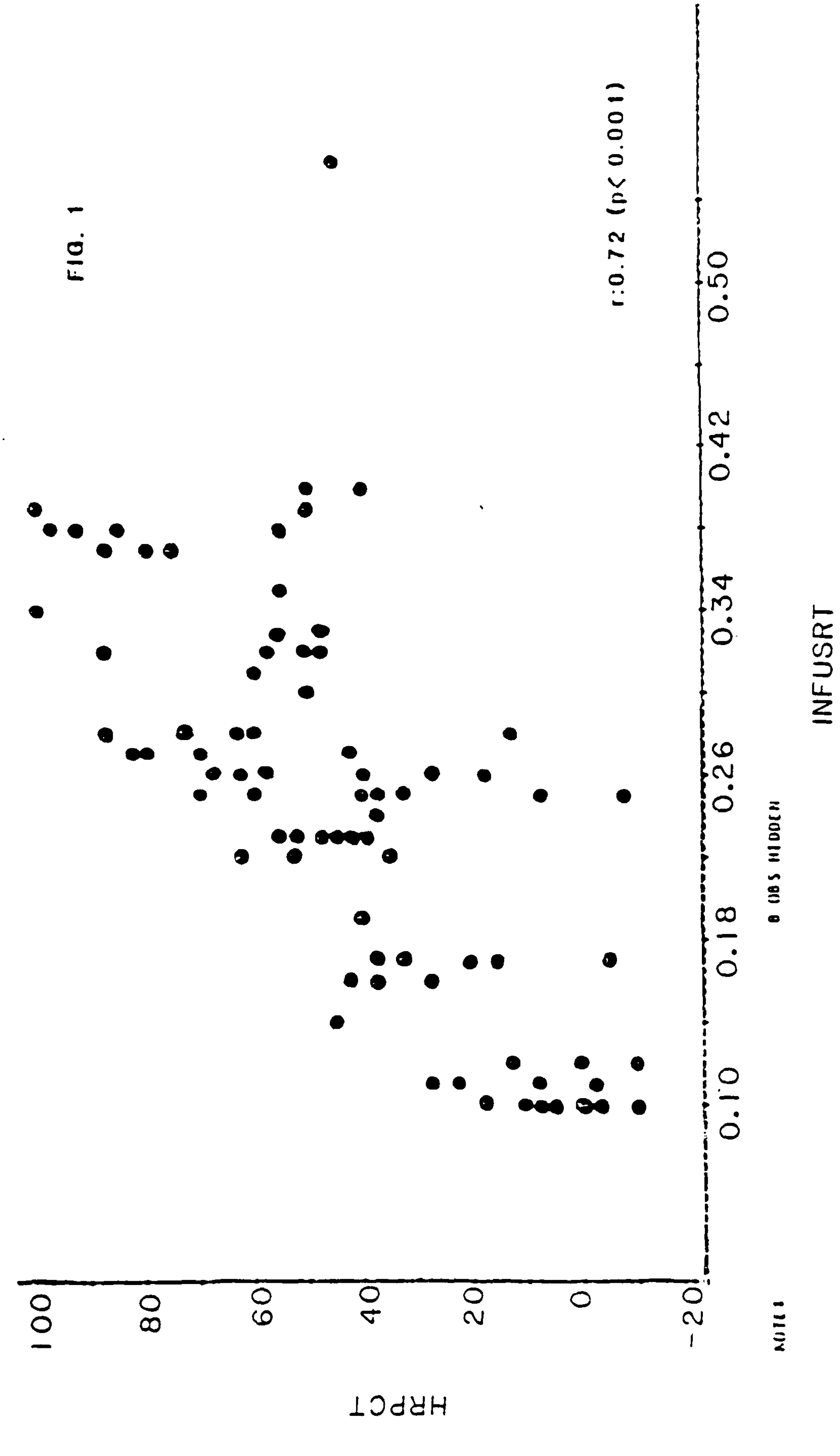


FIG. 1
r:0.72 (p< 0.001)
HRPCT
100
80
60
40
20
0
-20
INFUSRT
0.10
0.18
0.26
0.34
0.42
0.50
8 OBS HIDDEN
NOTE

FIG.2

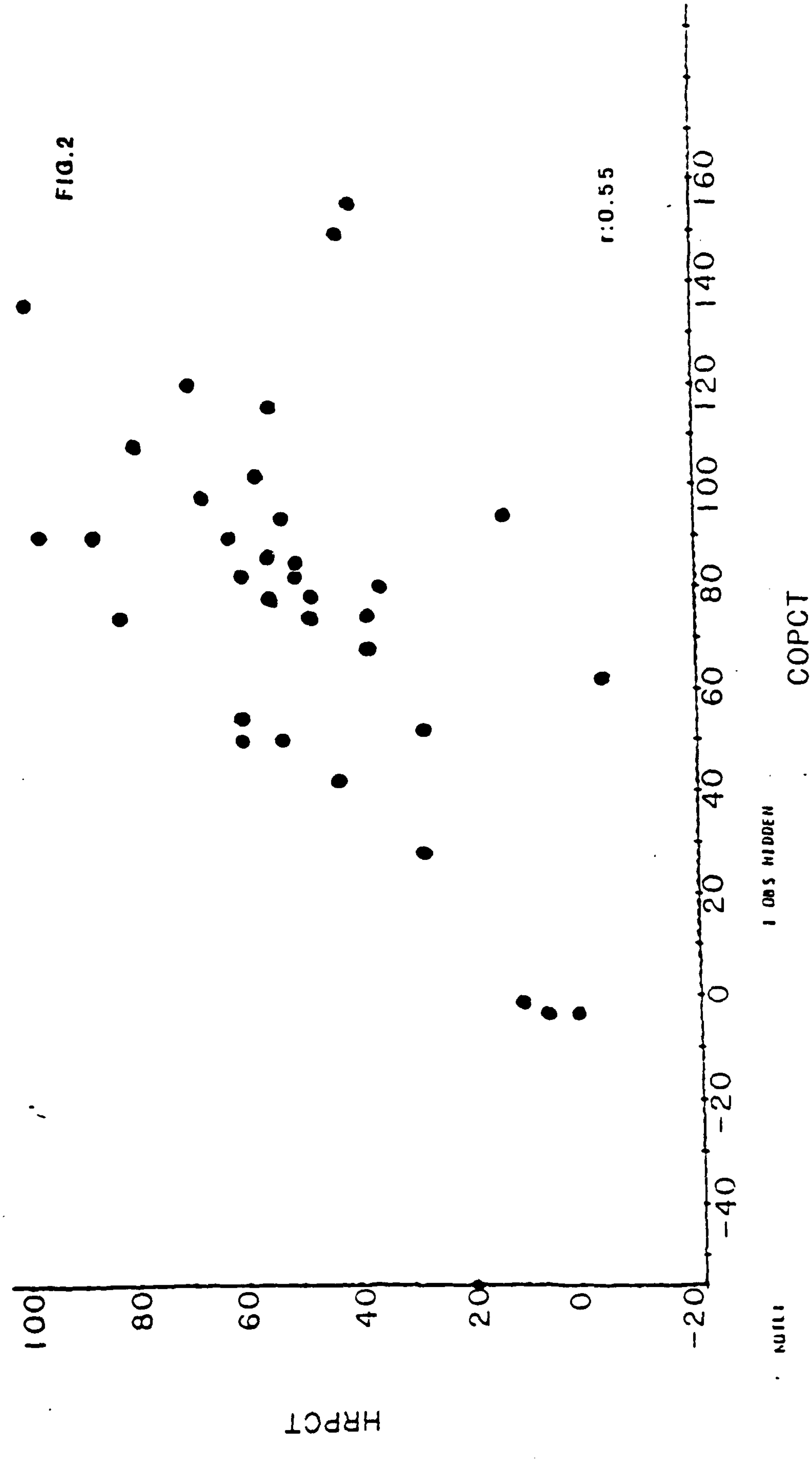
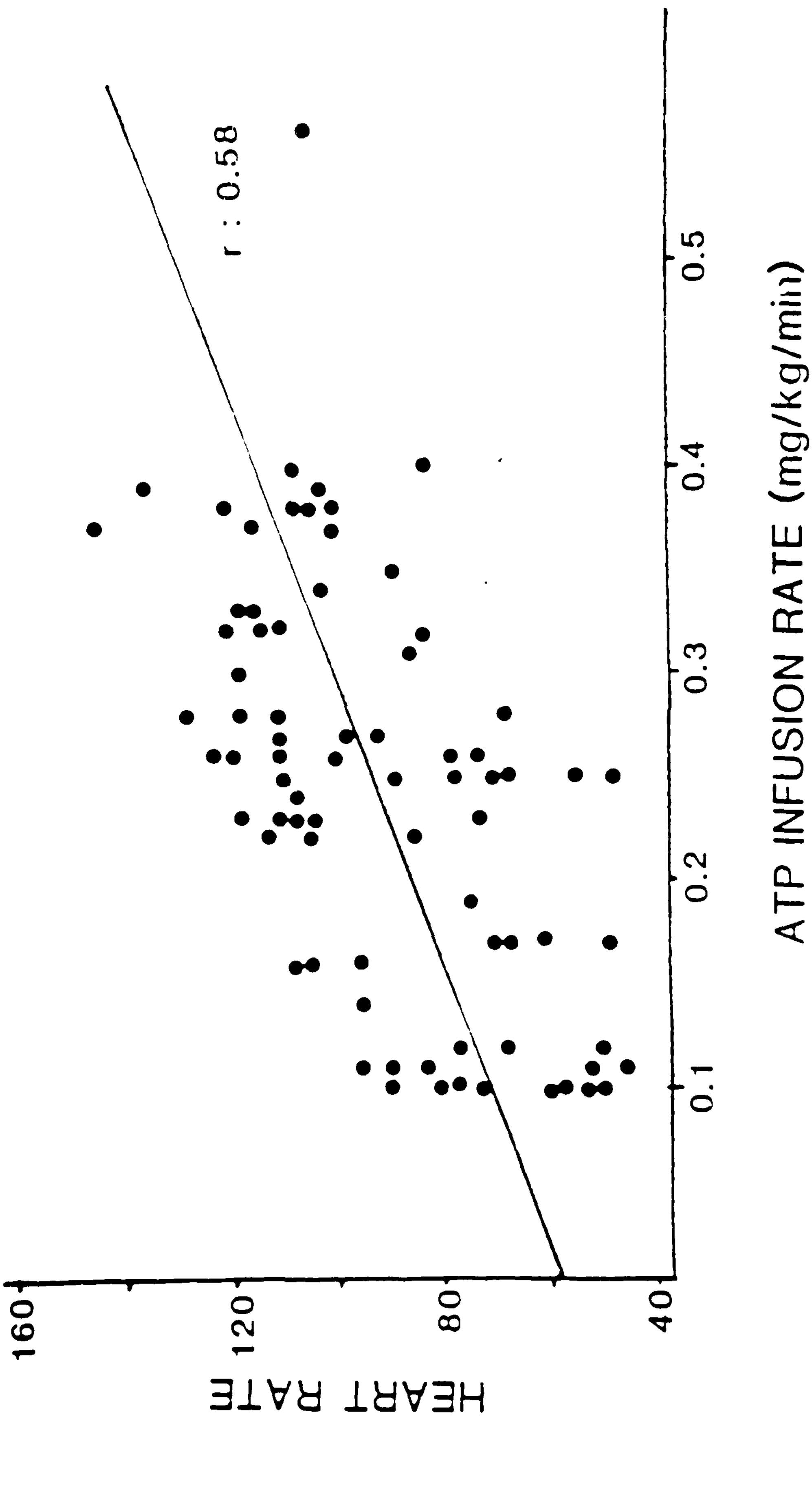

r:0.55
COPCT
HRPCT
1 OBS HIDDEN
-40 -20 0 20 40 60 80 100 120 140 160
-20 0 20 40 60 80 100

FIG.3


HEART RATE
160
120
80
40
0.1
0.2
0.3
0.4
0.5
ATP INFUSION RATE (mg/kg/min)
r : 0.58

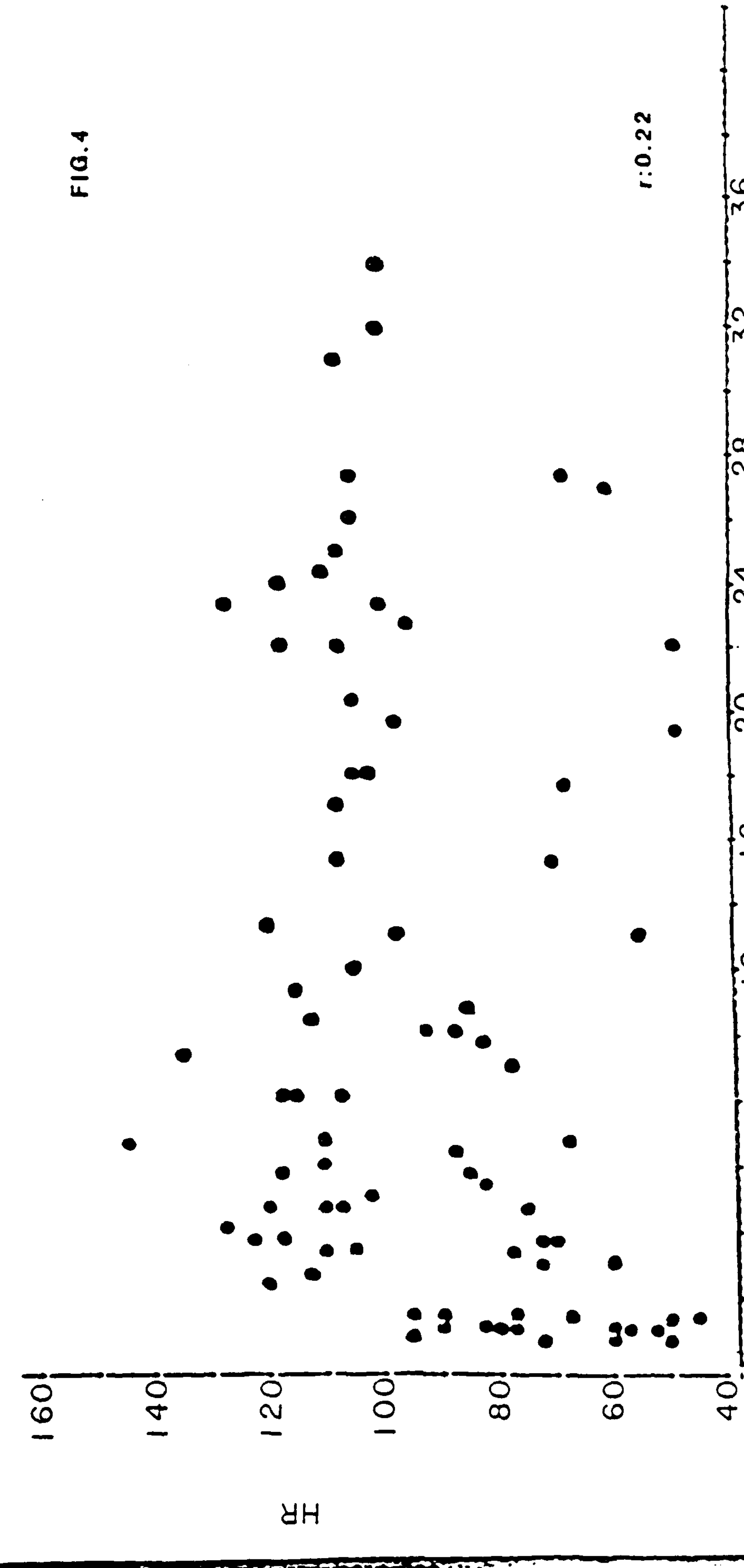


FIG.4
r:0.22
HR
160
140
120
100
80
60
40
0
4
8
12
16
20
24
28
32
36
TOTDOSE
4 OBS HIDDEN

FIG.5

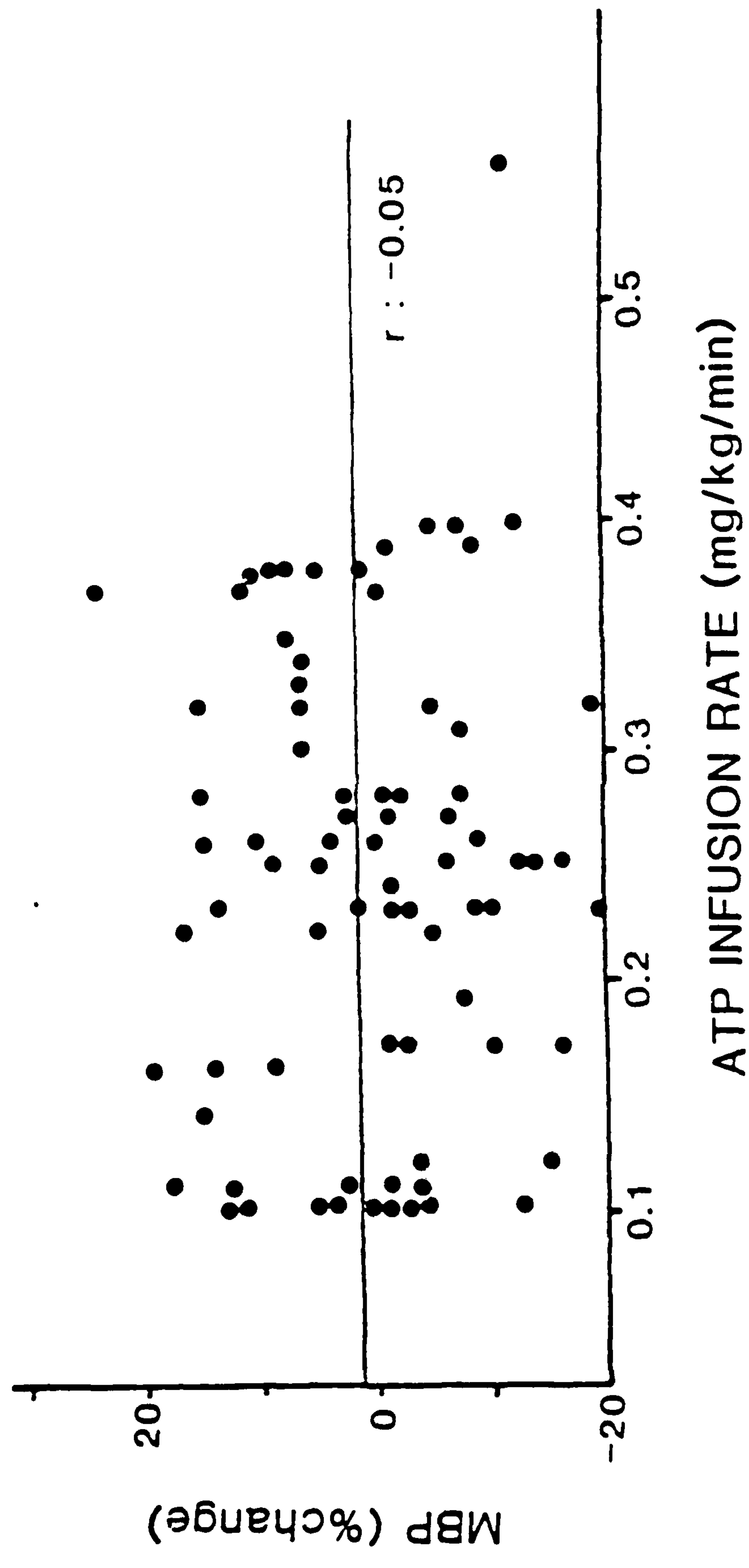

r : −0.05
MBP (%change)
20
0
−20
0.1
0.2
0.3
0.4
0.5
ATP INFUSION RATE (mg/kg/min)

FIG.6

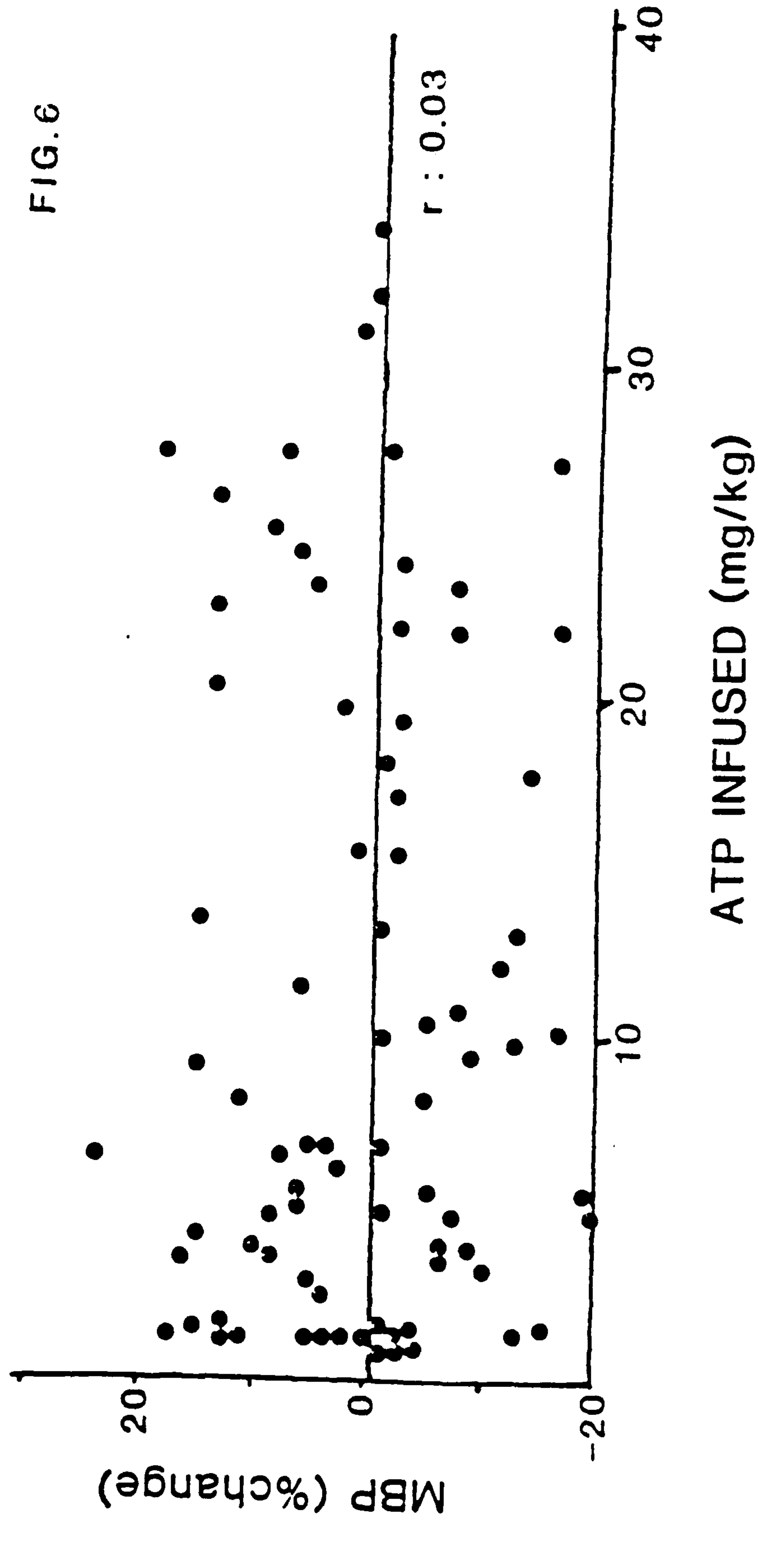


FIG.7

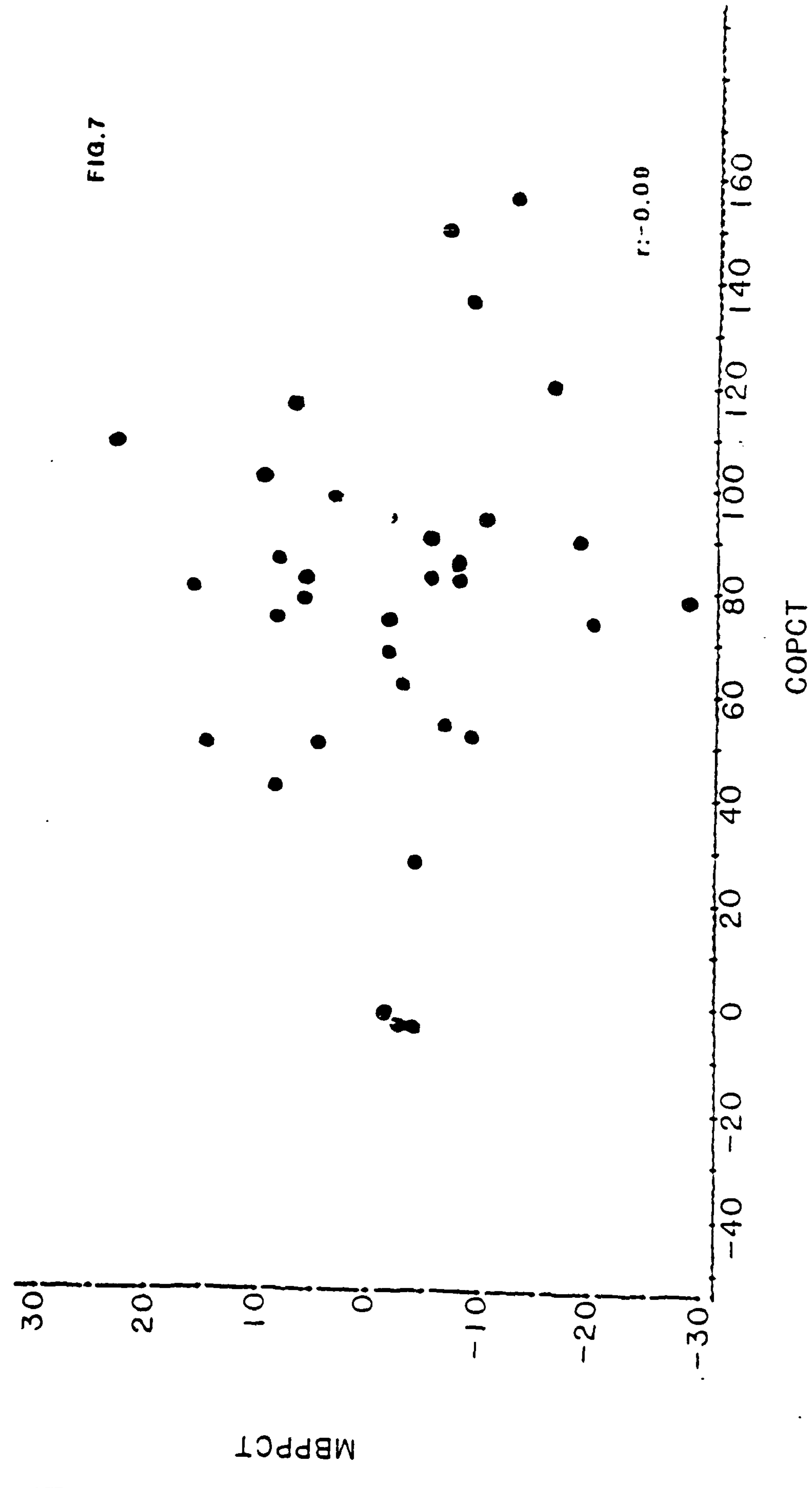

r:-0.00
COPCT
MBPPCT
-40
-20
0
20
40
60
80
100
120
140
160
30
20
10
0
-10
-20
-30

FIG. 8

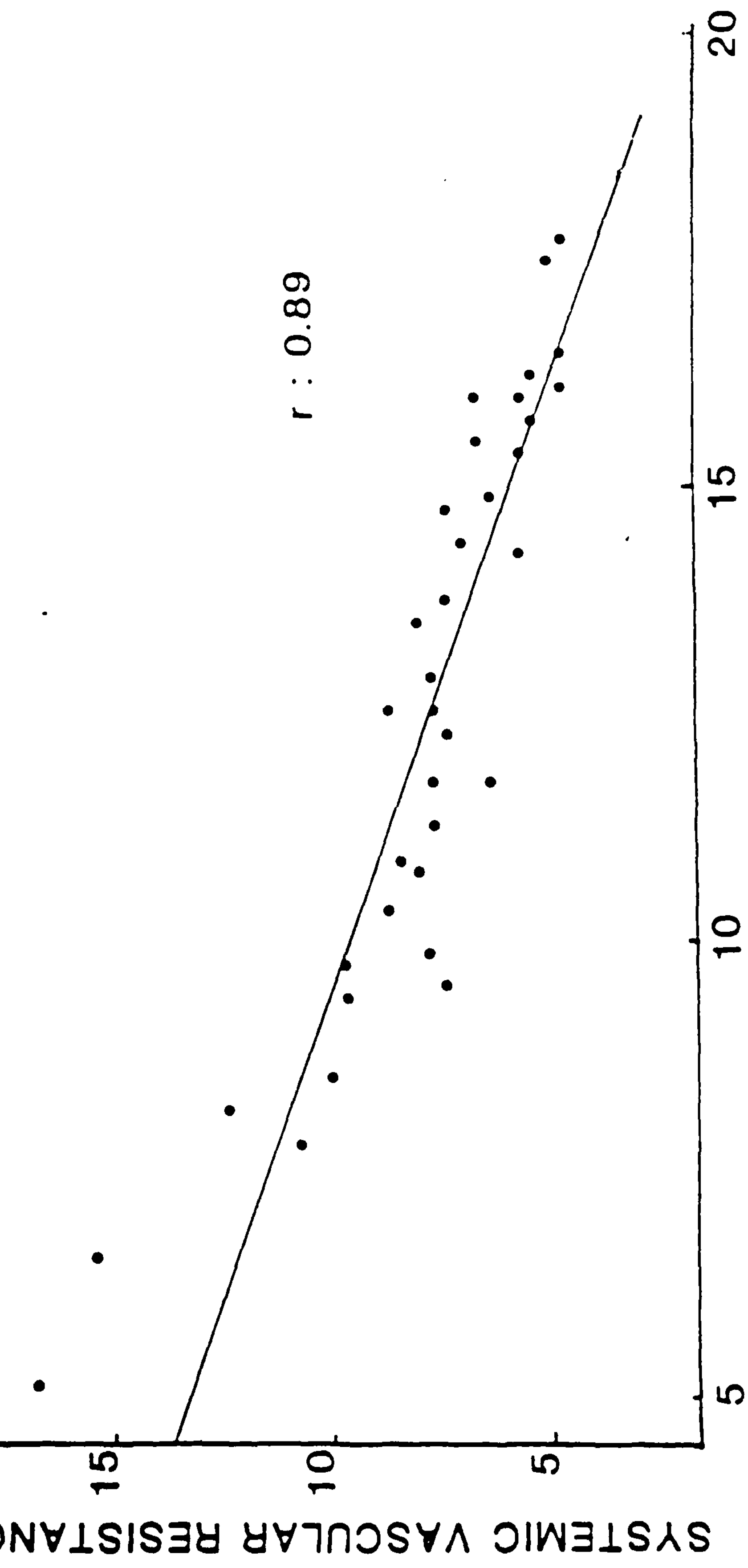

r : 0.89
SYSTEMIC VASCULAR RESISTANCE
15
10
5
CARDIAC OUTPUT
5
10
15
20

FIG.9

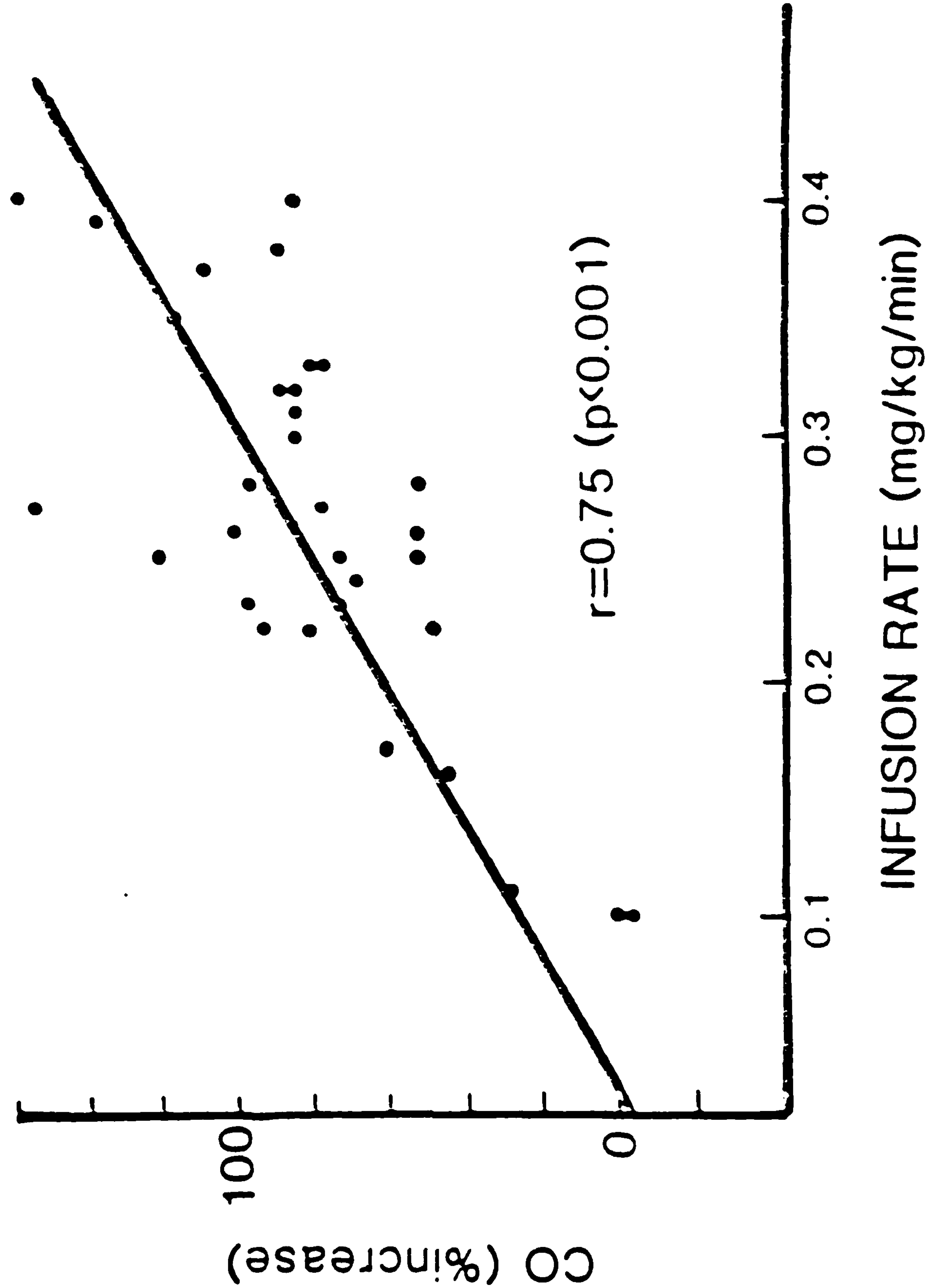
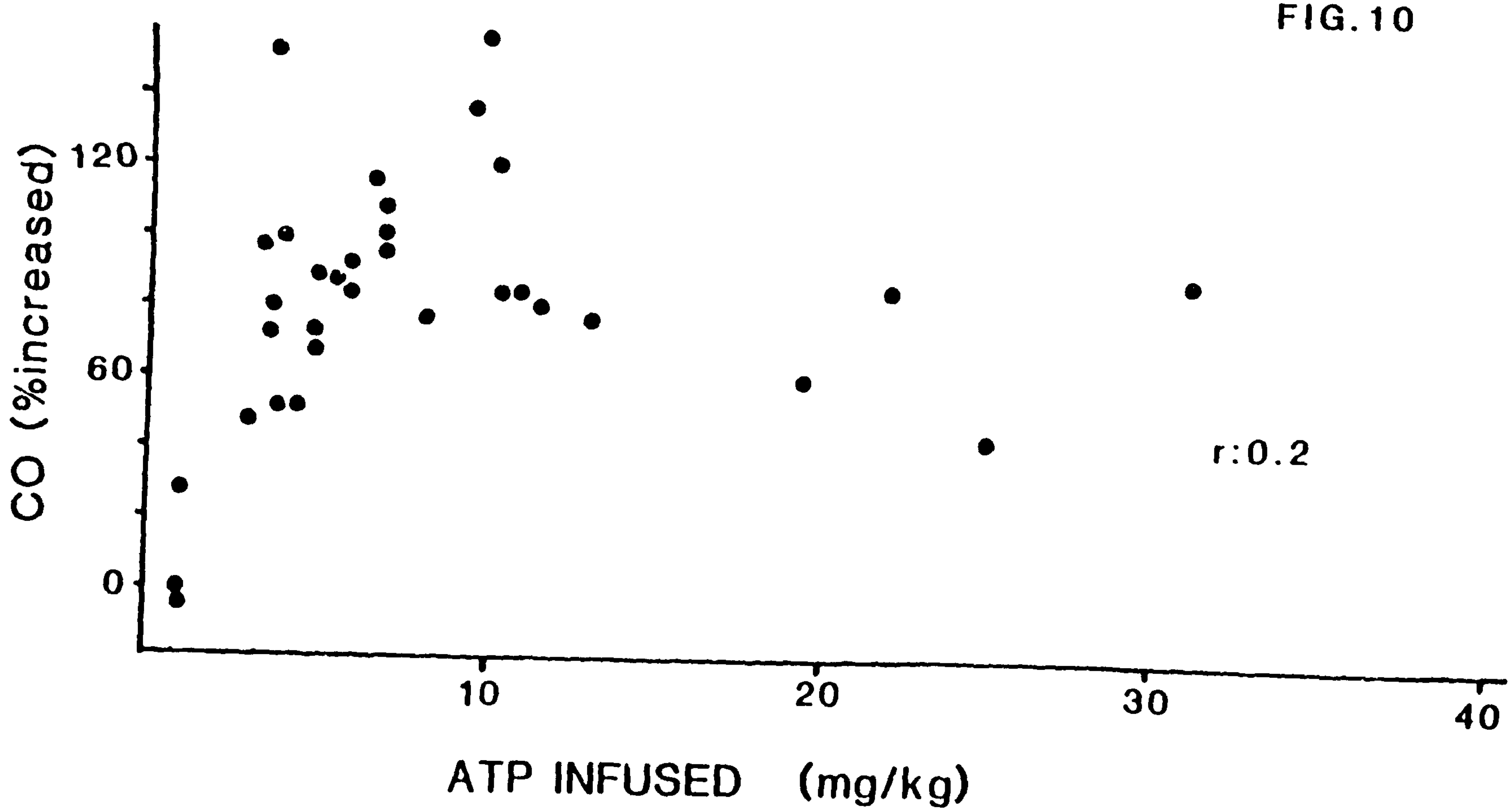

CO (%increase)
100
0
0.1
0.2
0.3
0.4
r=0.75 (p<0.001)
INFUSION RATE (mg/kg/min)

FIG. 10



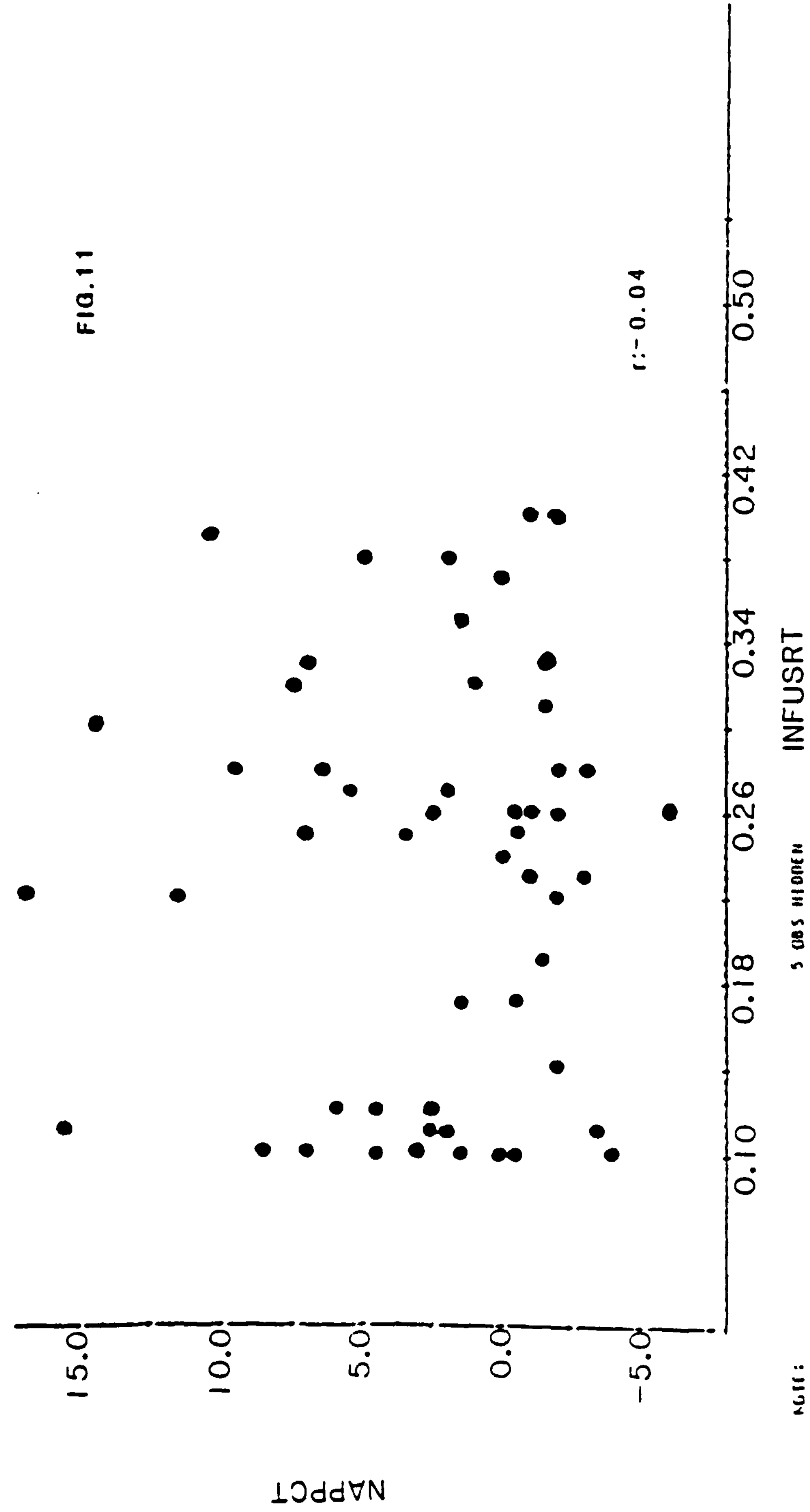


FIG.11
r=-0.04
NAPPCT
15.0
10.0
5.0
0.0
-5.0
0.10
0.18
0.26
0.34
0.42
0.50
INFUSRT
5 OBS HIDDEN
NOTE:

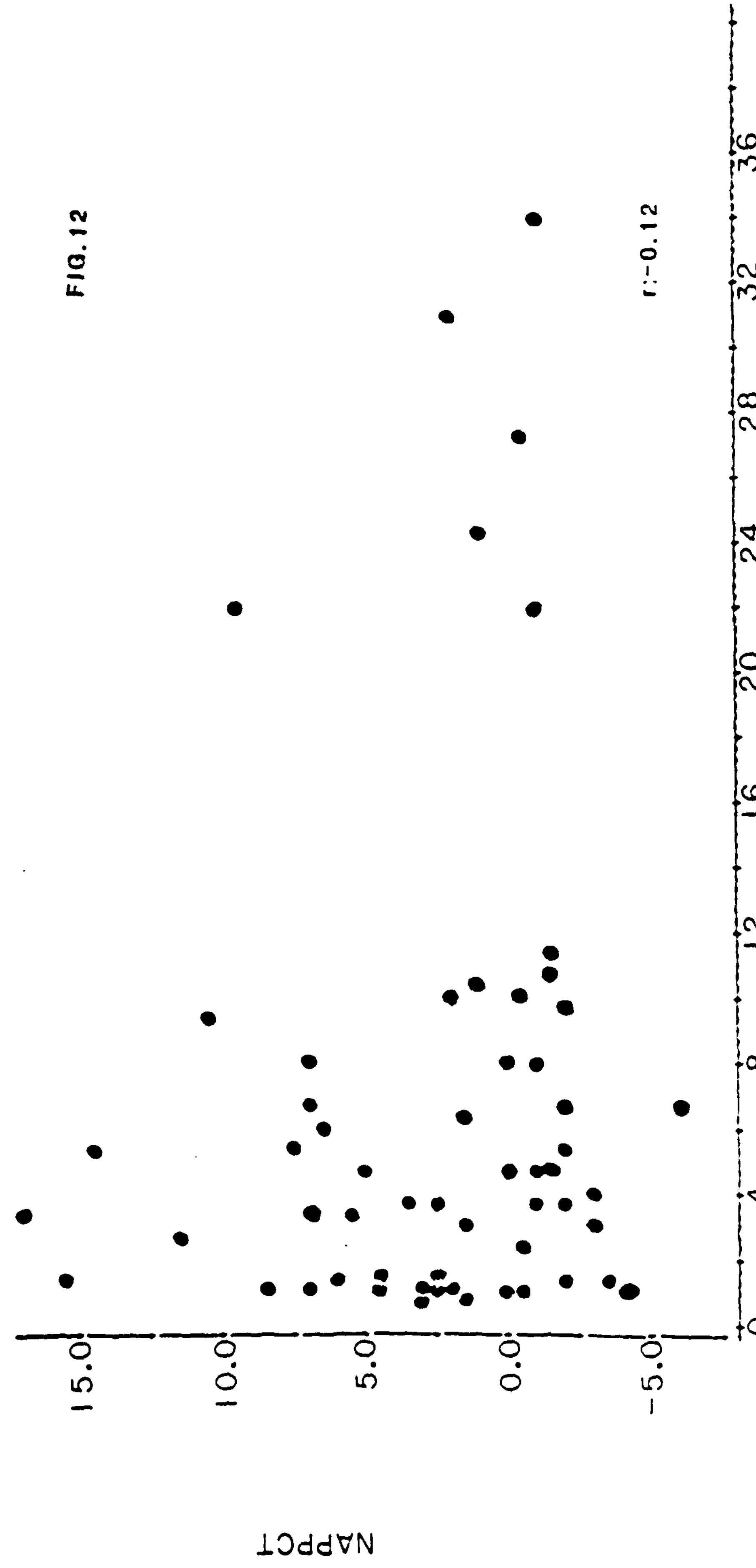


FIG.12
r:-0.12
TOTDOSE
NAPPCT
0
4
8
12
16
20
24
28
32
36
15.0
10.0
5.0
0.0
-5.0

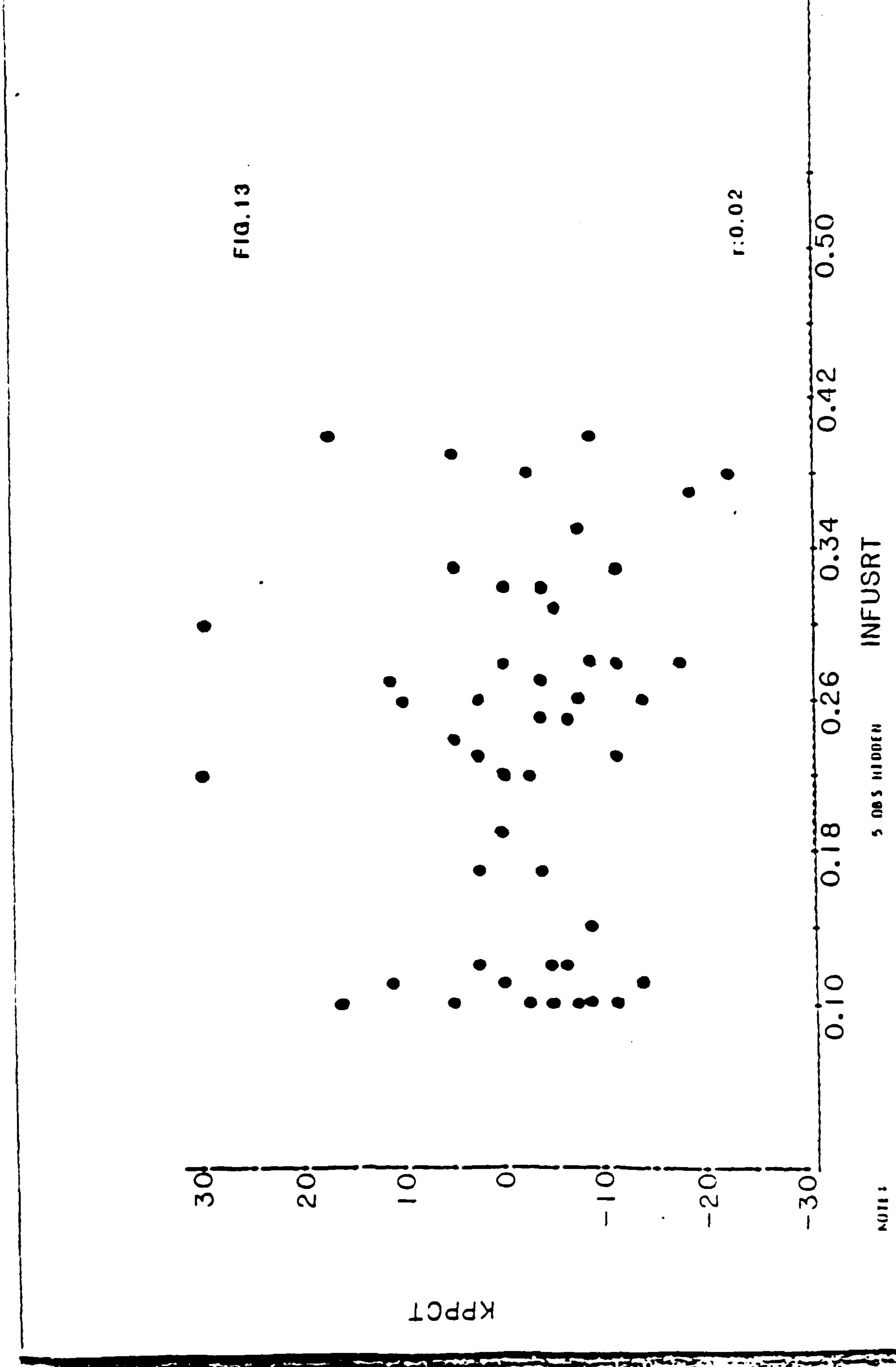


FIG.13
r:0.02
KPPCT
30
20
10
0
-10
-20
-30
INFUSRT
0.10
0.18
0.26
0.34
0.42
0.50
NOTE:
5 OBS HIDDEN

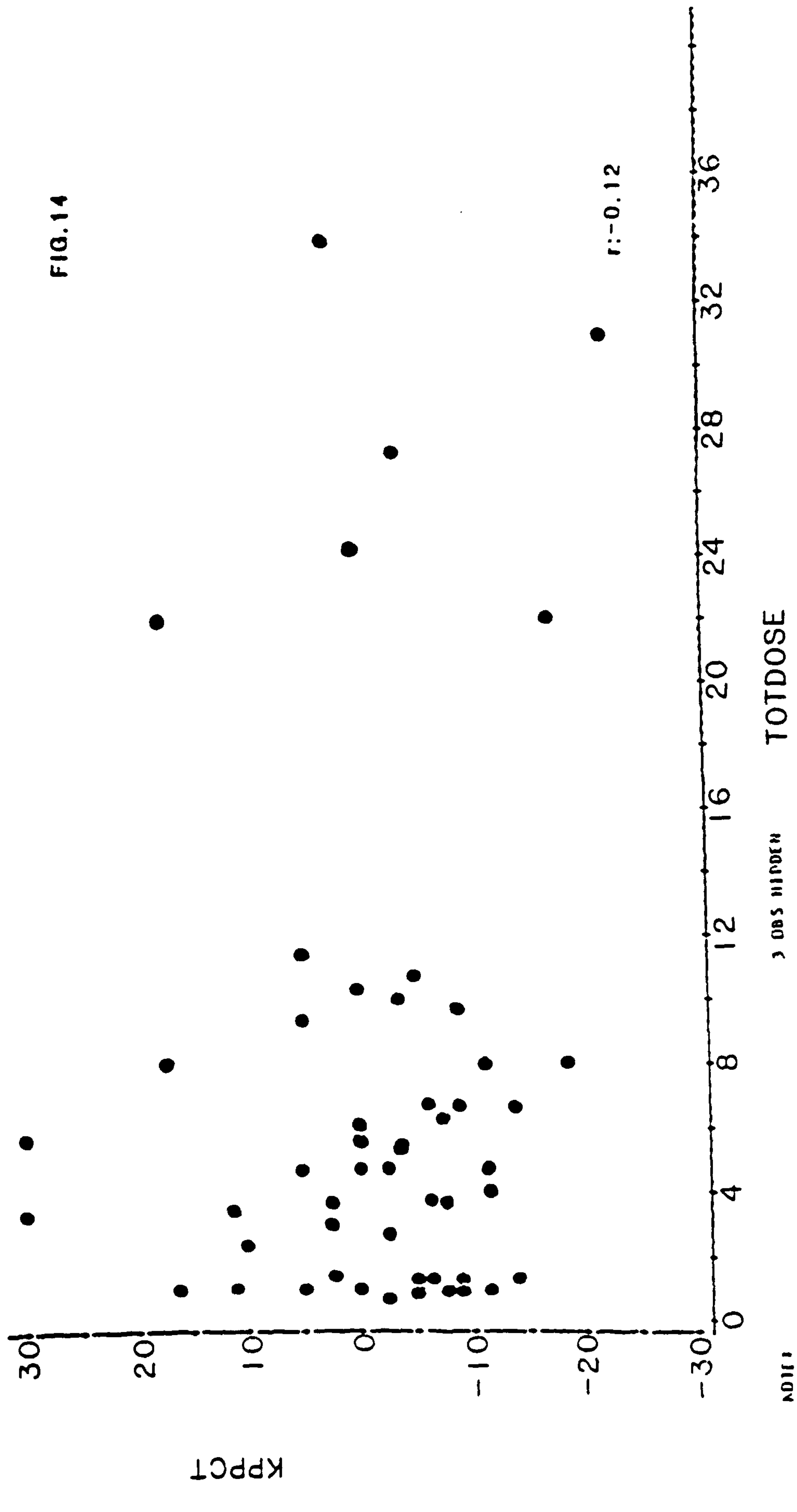
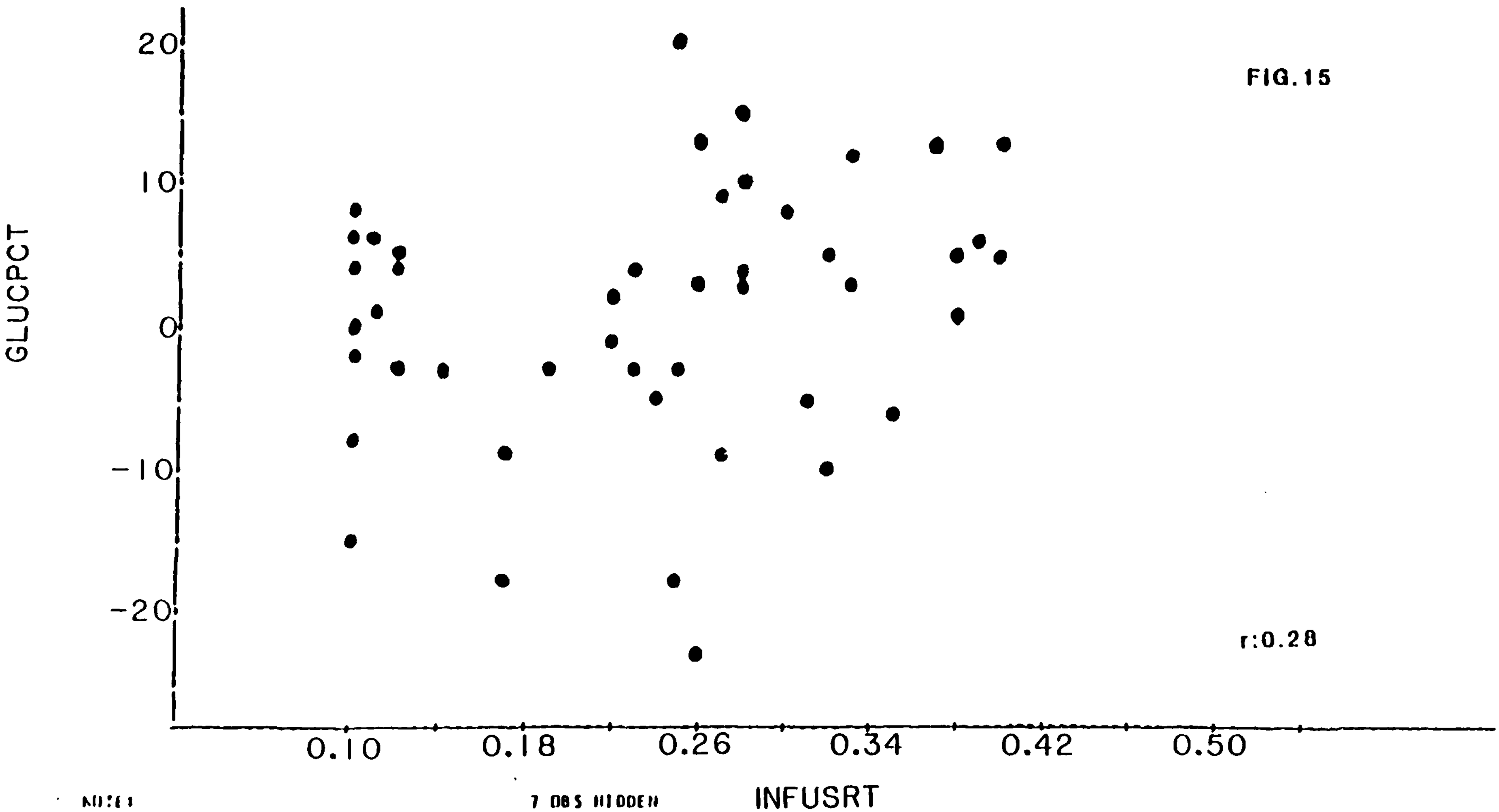

r:-0.12
3 OBS HIDDEN
TOTDOSE
KPPCT
30
20
10
0
-10
-20
-30
0
4
8
12
16
20
24
28
32
36

FIG.14

FIG. 15


GLUCPCT
20
10
0
-10
-20
0.10
0.18
0.26
0.34
0.42
0.50
INFUSRT
7 OBS HIDDEN
r:0.28

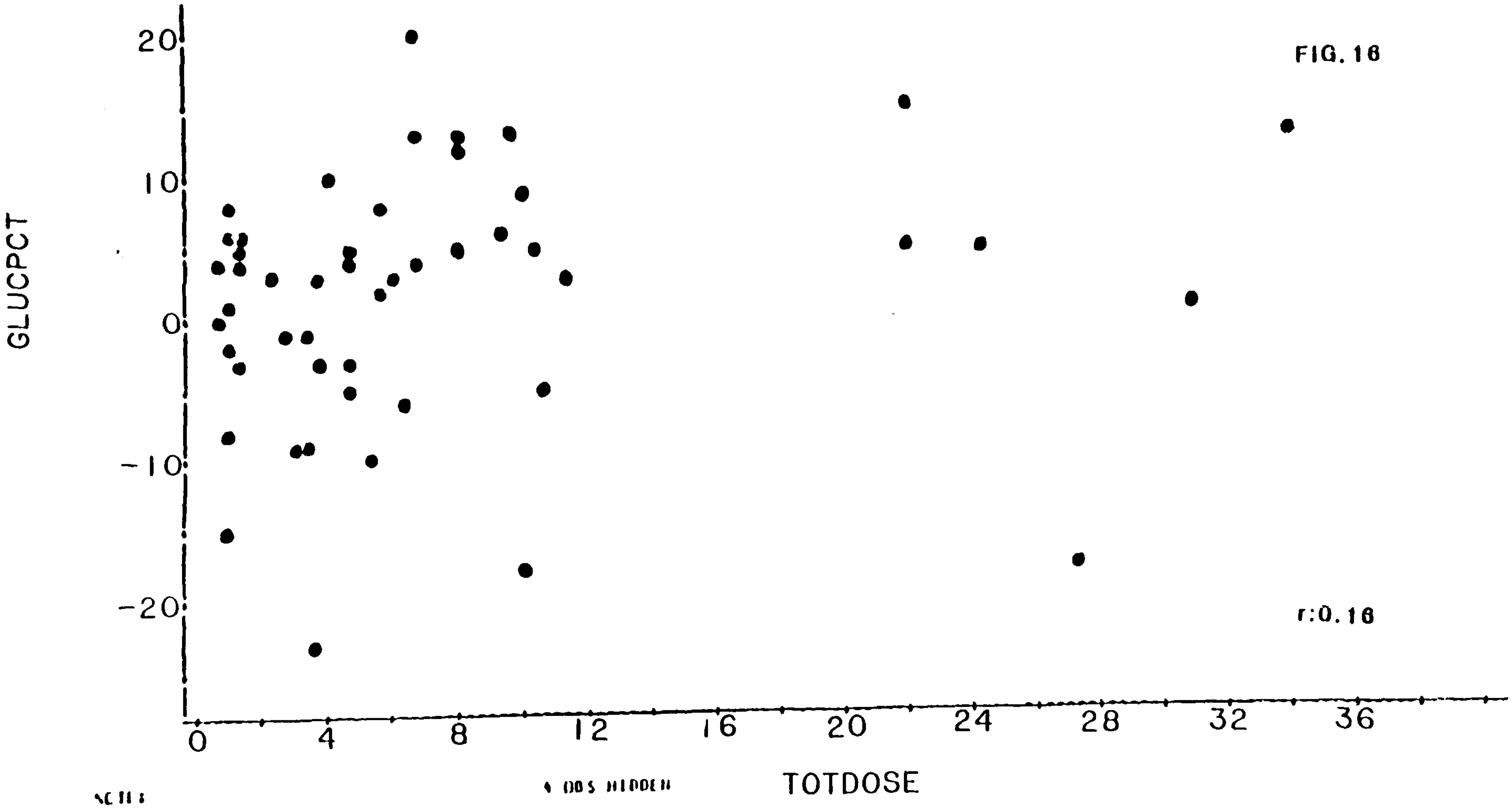
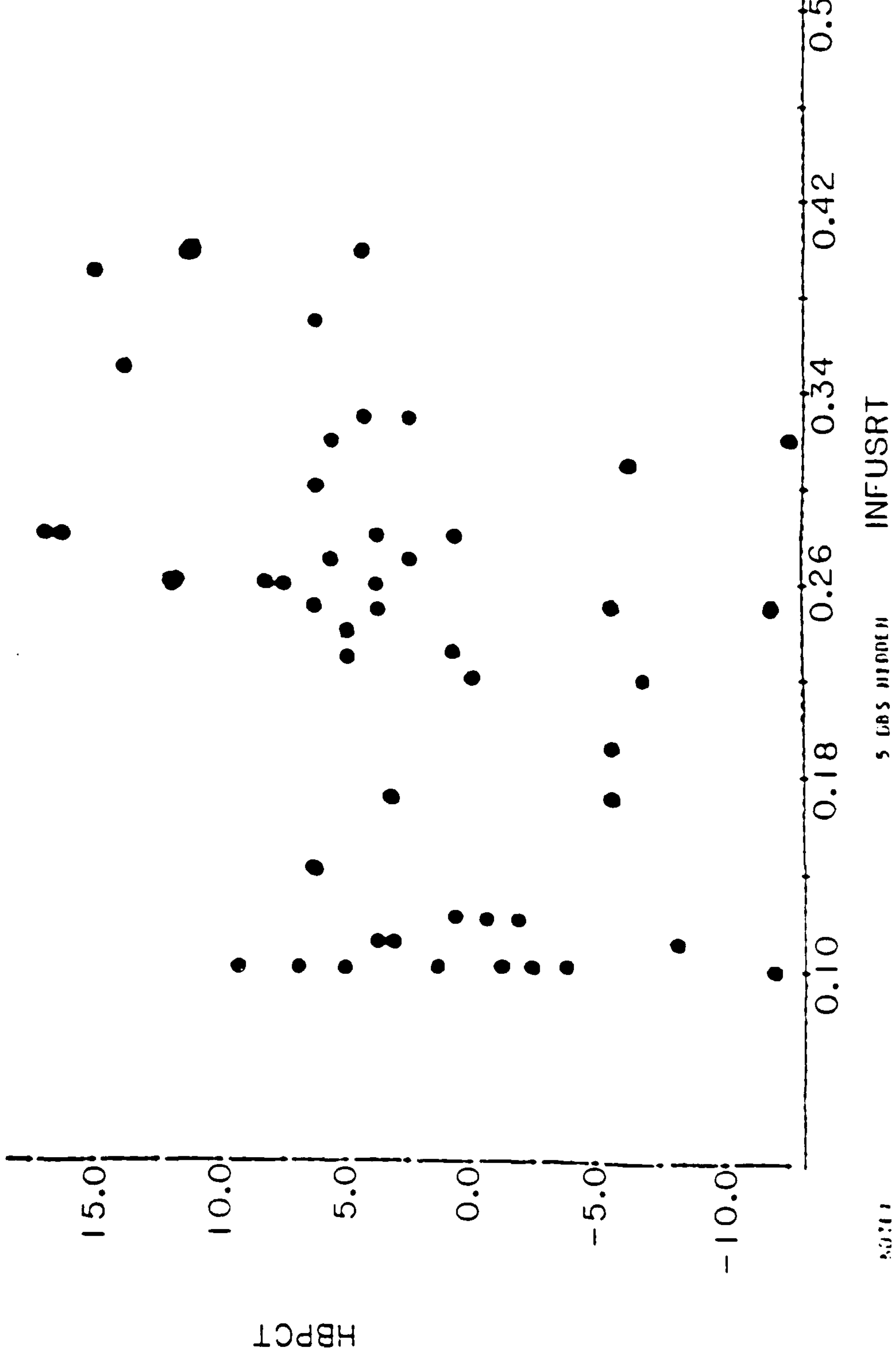

GLUCPCT
20
10
0
-10
-20
0
4
8
12
16
20
24
28
32
36
TOTDOSE
OBS HIDDEN
r:0.16

FIG. 16

FIG. 17


r:0.35
HBPCT
15.0
10.0
5.0
0.0
-5.0
-10.0
0.10
0.18
0.26
0.34
0.42
0.50
INFUSRT
5 OBS HIDDEN

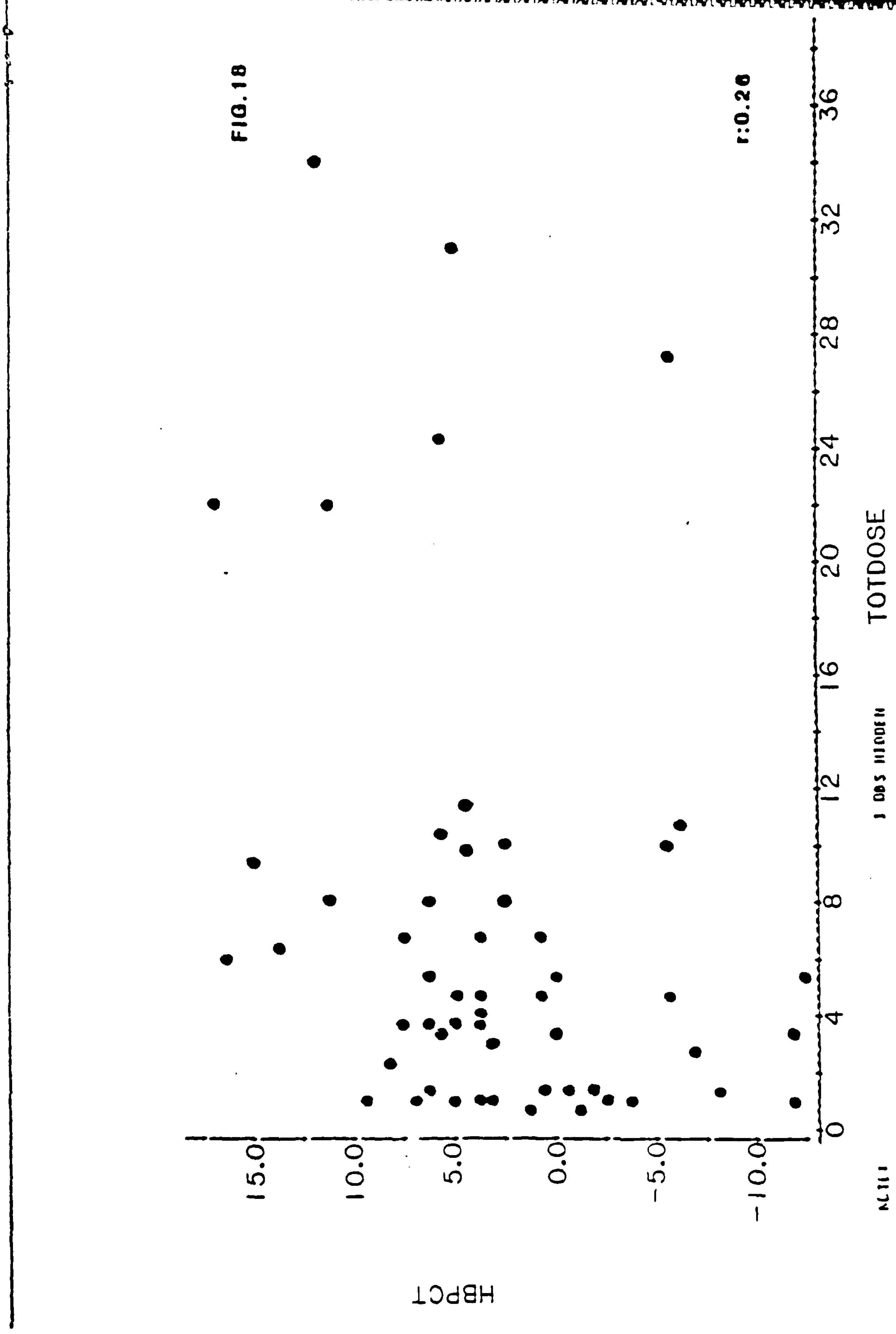

r:0.26
HBPCT
15.0
10.0
5.0
0.0
-5.0
-10.0
0
4
8
12
16
20
24
28
32
36
TOTDOSE
1 OBS HIDDEN

FIG.18

END

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